

Breakthrough Therapy Designation: Exploring the Qualifying Criteria

Park Hyatt Hotel • Washington, DC
Friday, April 24, 2015



CDER Breakthrough Therapy Designation: Two-and-a-Half Years In

Office of Strategic Programs/Office of Program and Strategic Analysis
FDA/Center for Drug Evaluation and Research

4/24/15

BT Program at a Glance

On July 9, 2012 the Food and Drug Administration Safety and Innovation Act (FDASIA) was signed; this included the Breakthrough Therapy Designation

To qualify for the designation, a drug must...

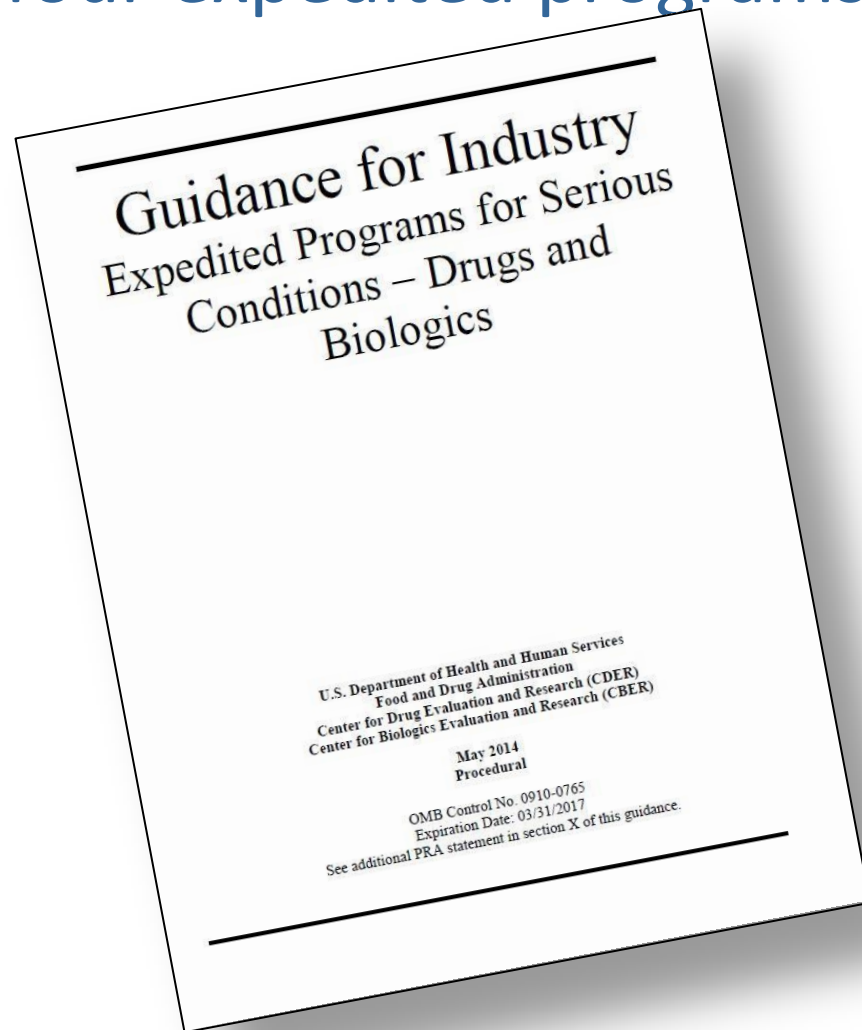
- Treat a **serious** or **life threatening** disease or condition
- Provide preliminary clinical evidence indicating a **potential for substantial improvement** over existing therapies on one or more clinically significant endpoints

A drug with a Breakthrough designation will have...

- Increased communication with FDA during drug development and review
- FDA guidance to ensure that the design of clinical trials are as efficient as practicable
- A cross-disciplinary project lead assigned to the FDA review team and increased involvement of senior managers and experienced review staff

Breakthrough is one of four expedited programs

- Final Guidance issued in March 2014 defines each program, requirements, benefits
- Accelerated Approval
- Fast Track
- Priority Review
- Breakthrough Therapy



This evaluation provides insight into designation decision criteria and characteristics of grants, denials

- This evaluation covers the designation phase of the Breakthrough (BT) program and analyzes Breakthrough Therapy Designation Request (BTDR) decisions and withdrawals from Sept. 2012 – Dec 2014
- A separate workload evaluation of the breakthrough program is ongoing

Administrative Characteristics

- What are the key characteristics of BTDRs?

Decision Factors

- Are there key decision factors for granting or denying a BTDR?

Breakthrough Standard

- Is there a definable threshold for substantial improvement?

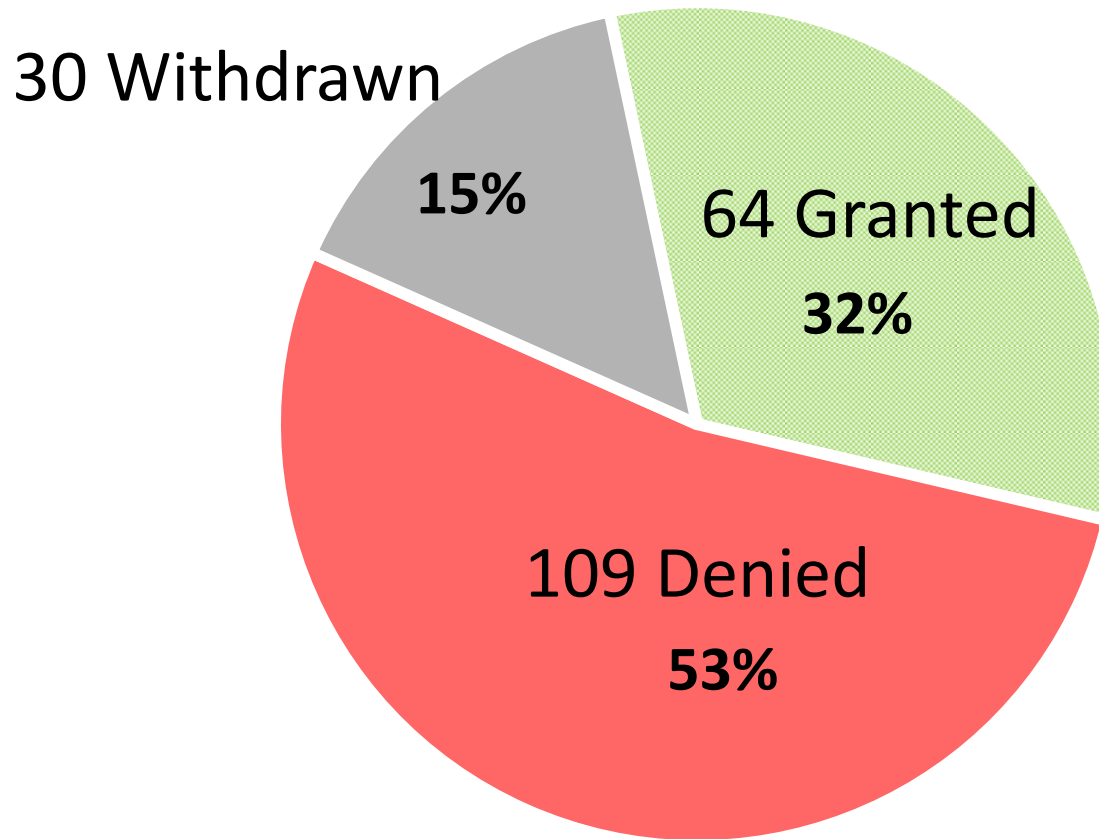
Evaluation of CDER's Breakthrough Therapy (BT) Program: Designation Phase

Report outline

- I. Program overview
- II. Trial evidence analysis
- III. OHOP treatment effect case study
- IV. Denial and withdrawal rationales analysis
- V. Conclusion
- VI. Appendices

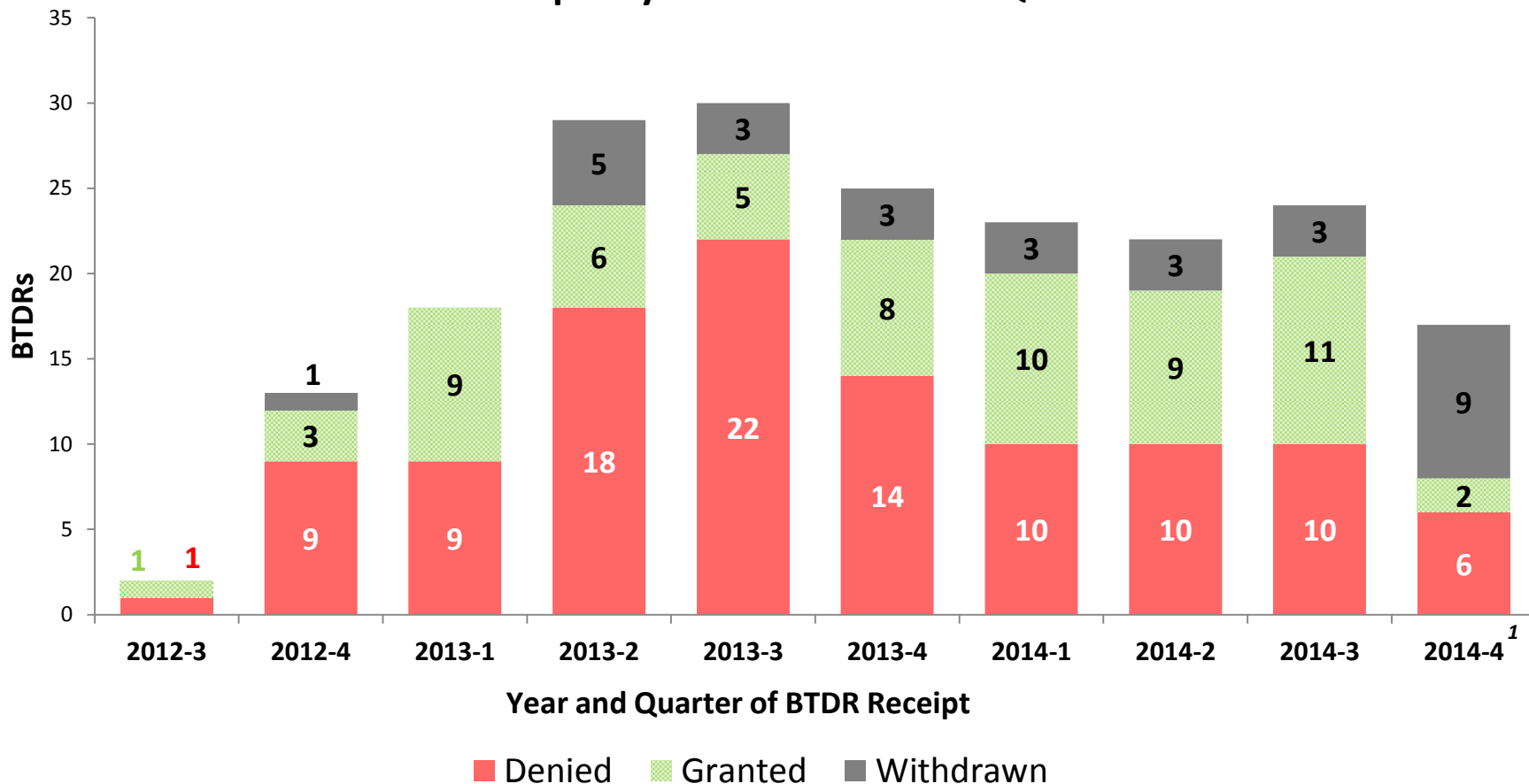
I. Program Overview: What Does the Breakthrough Program Look Like to Date?

CDER granted, denied or received withdrawals for 203 BTDRs from 2012 through 2014



Sponsor interest in the breakthrough program has been fairly constant over time

BTDR Receipts by Calendar Year and Quarter

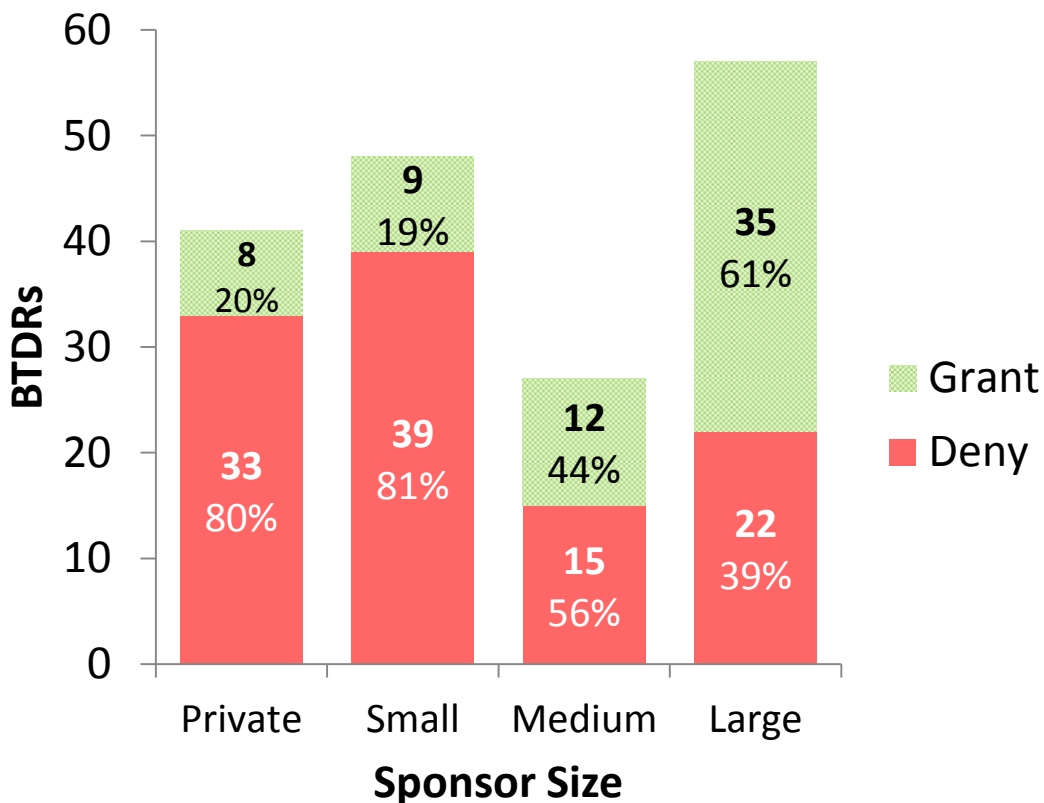


¹Excludes BTDRs pending as of Dec. 31, 2014

“Large” sponsors submitted over half the granted BTDRs

- We define sponsors by number of employees:
 - Large = >15,000
 - Medium = 250-15,000
 - Small = <250
 - Privately held
- Small & privately held sponsors submitted 50% of BTDRs but only received 25% of grants
- 15% of private and small sponsors had regulatory experience² compared to 83% of medium and large sponsors
- 78% of sponsors are from the US

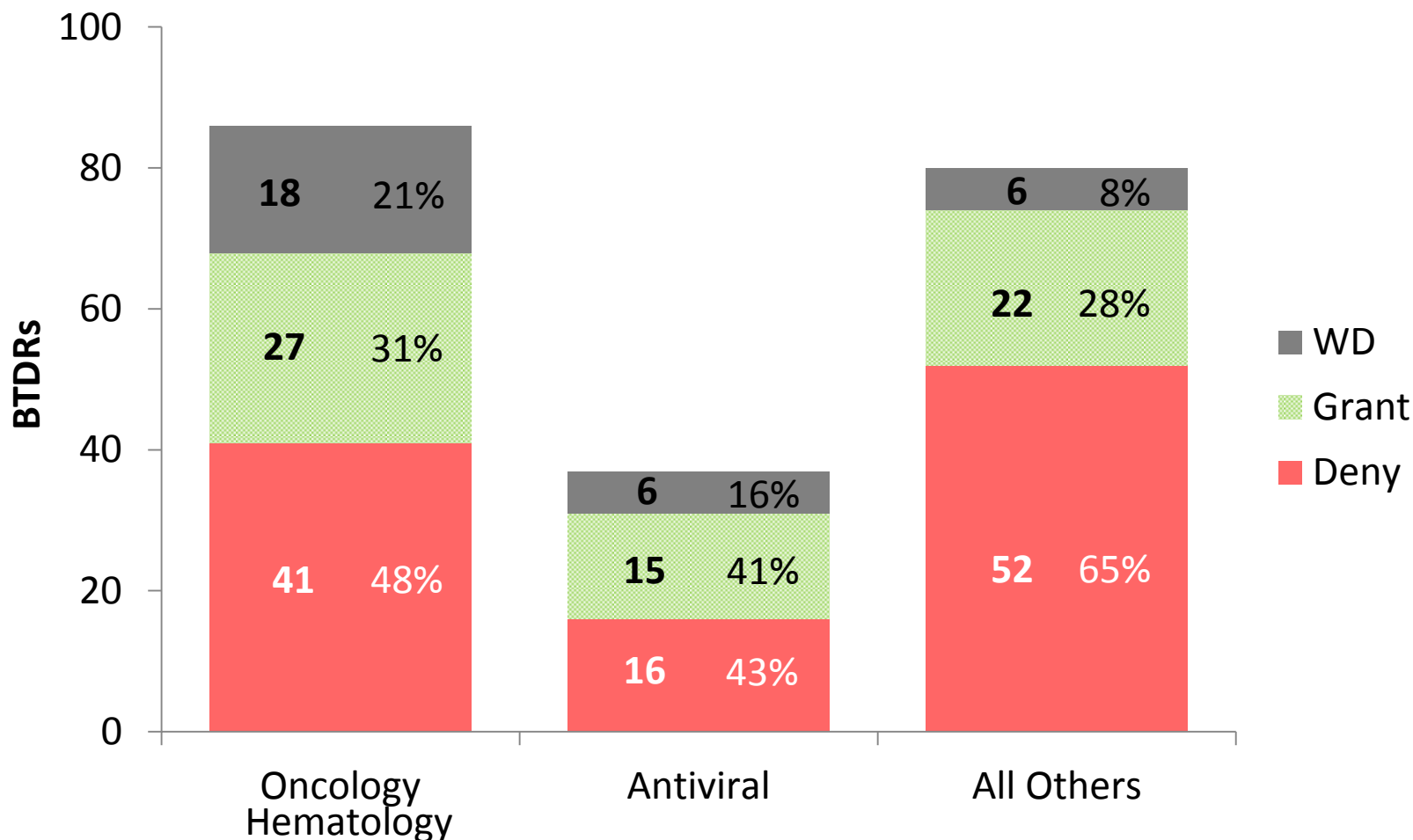
BTDR Decisions by Sponsor Size ¹



¹Sponsor size reflects that of the parent company, if applicable. Private sponsors also included sponsors that did not have any sponsor data available in the FDA DUNS database.

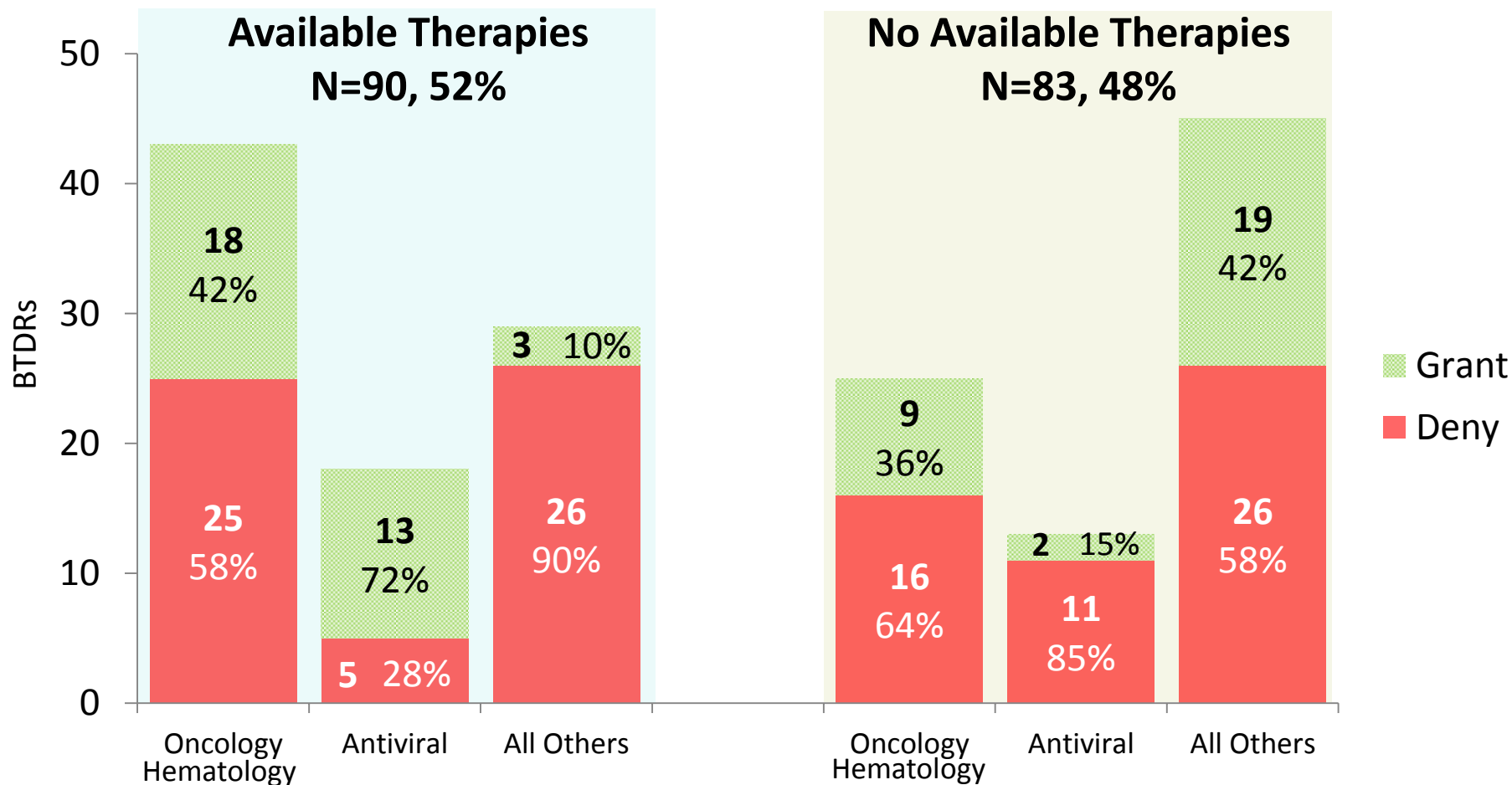
²Regulatory experience is based on whether the parent company of the sponsor (or sponsor itself) had a drug listed in the Orange Book at the time of submitting a BTDR.

The majority of requests were for oncology/hematology or antiviral drugs; antivirals had the highest proportion of grants



¹Excludes pending requests

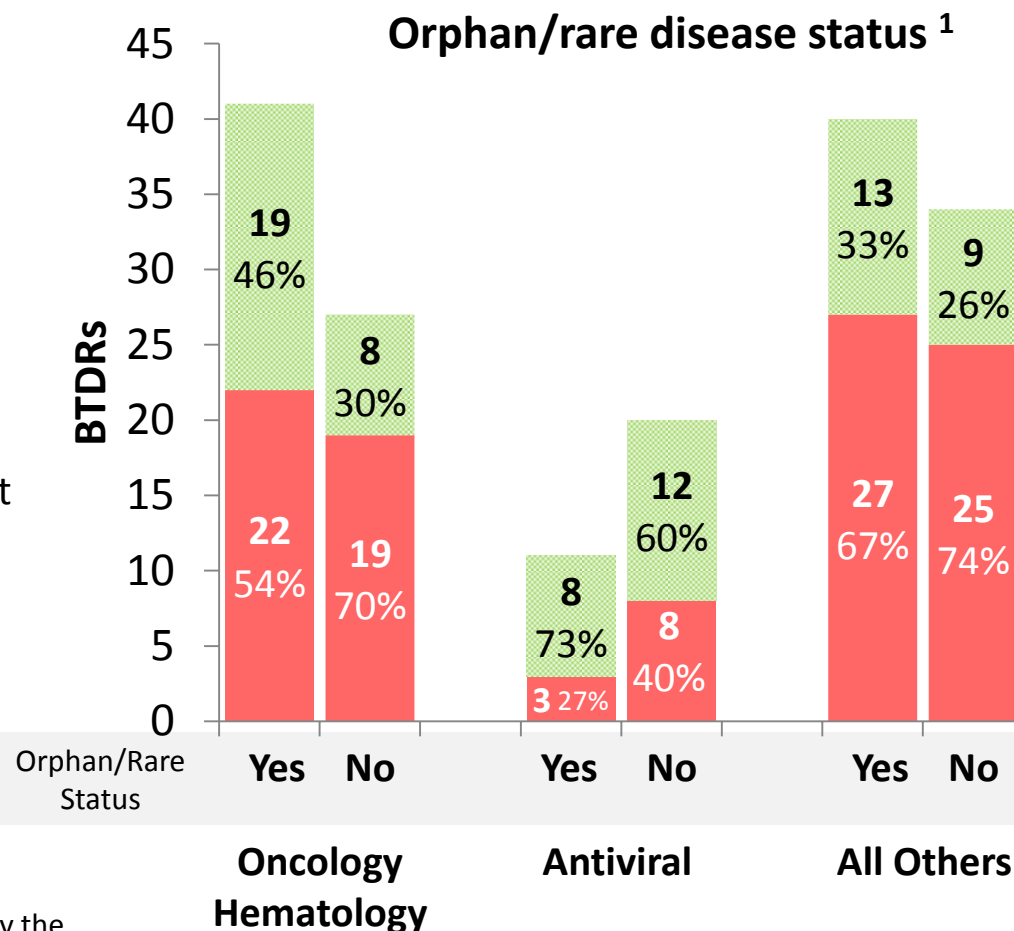
Grants and denials were closely split overall with respect to available therapies¹, but this varied by therapeutic class



¹ As defined by the guidance for industry [Expedited Programs for Serious Conditions – Drugs and Biologics](#).

BTDRs for orphan/rare diseases did not have a higher proportion of grants

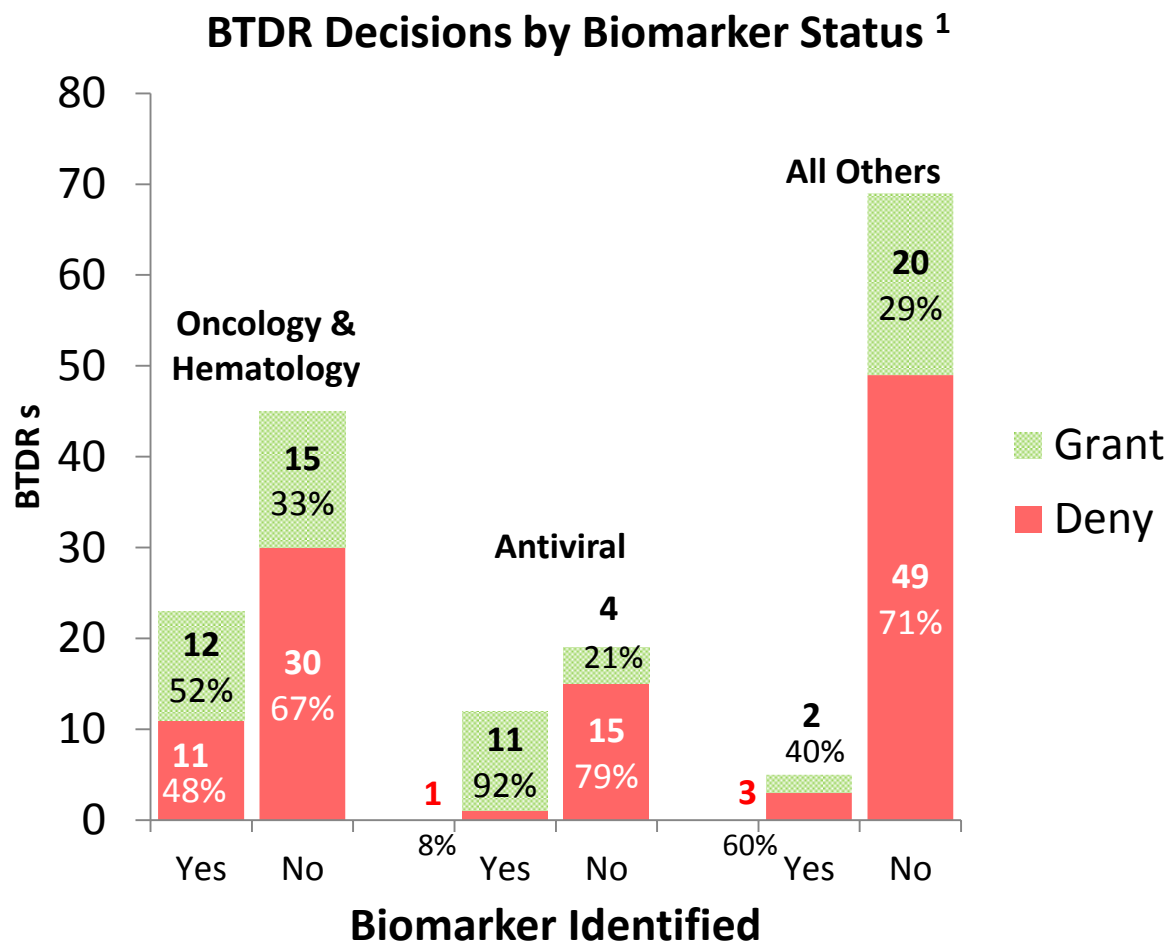
- 55% of granted BTDRs and 52% of denied BTDRs were for orphan or rare disease drugs
- The highest percentage of rare/orphan BTDRs were for oncology and hematology drugs
- There was no notable difference between the two groups in the highest trial phase submitted as evidence
- BTDRs for orphan/rare-designated drugs tended to have fewer patients enrolled in trials, which is expected given rarity of the indication



¹Consists of drugs who applied for and received [orphan designation](#) from the FDA and/or diseases categorized by the FDA as rare (affecting <200,000 people in the US).

BTDRs with biomarkers in their indication had a higher proportion of grants

- Approximately a quarter of BTDRs had a prognostic biomarker in their indications
- 65% of BTDRs with prognostic biomarkers in their indications were granted compared to 29% of those that did not
- High percentage of oncology, hematology and antiviral BTDRs with biomarkers may reflect era of precision medicine

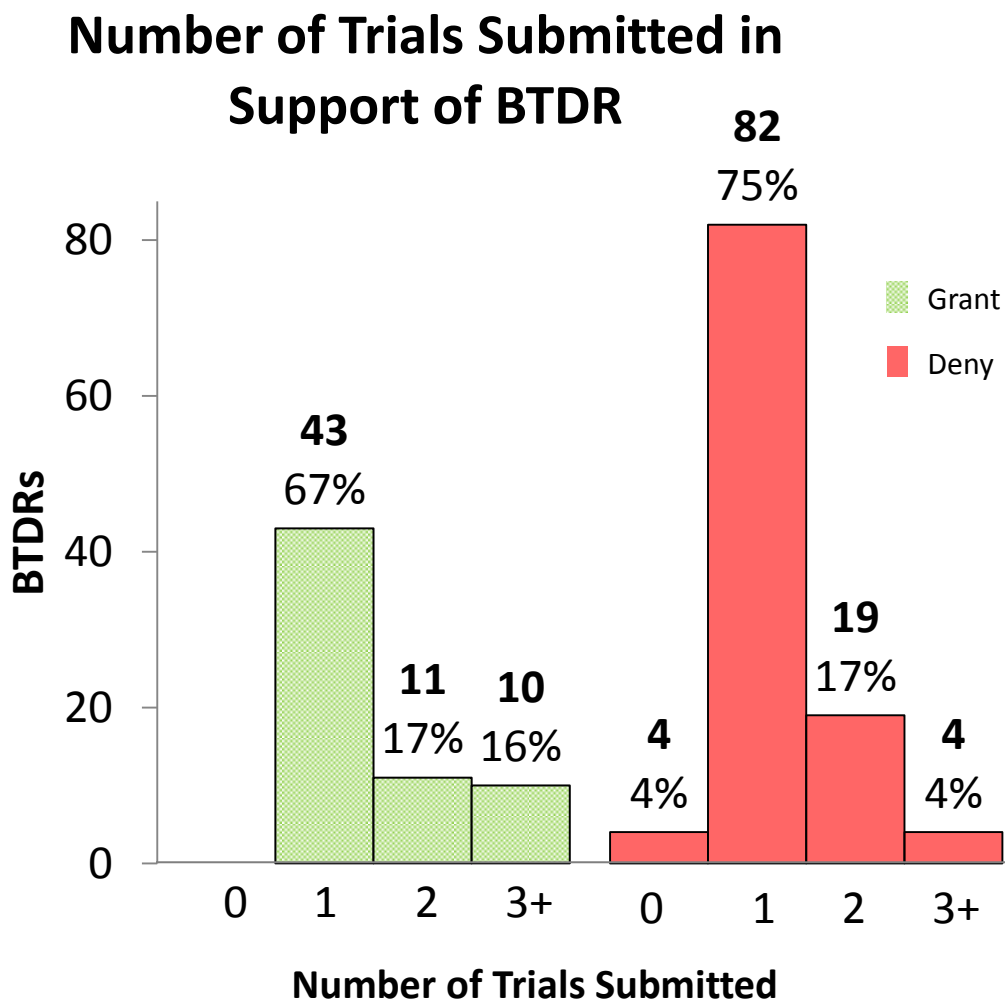


¹Prognostic biomarker is defined in the [Guidance for Industry and FDA Staff: Qualification Process for Drug Development Tools](#)

II. Trial Evidence Analysis: What Type and Level of Evidence are Needed to Support a Breakthrough Designation?

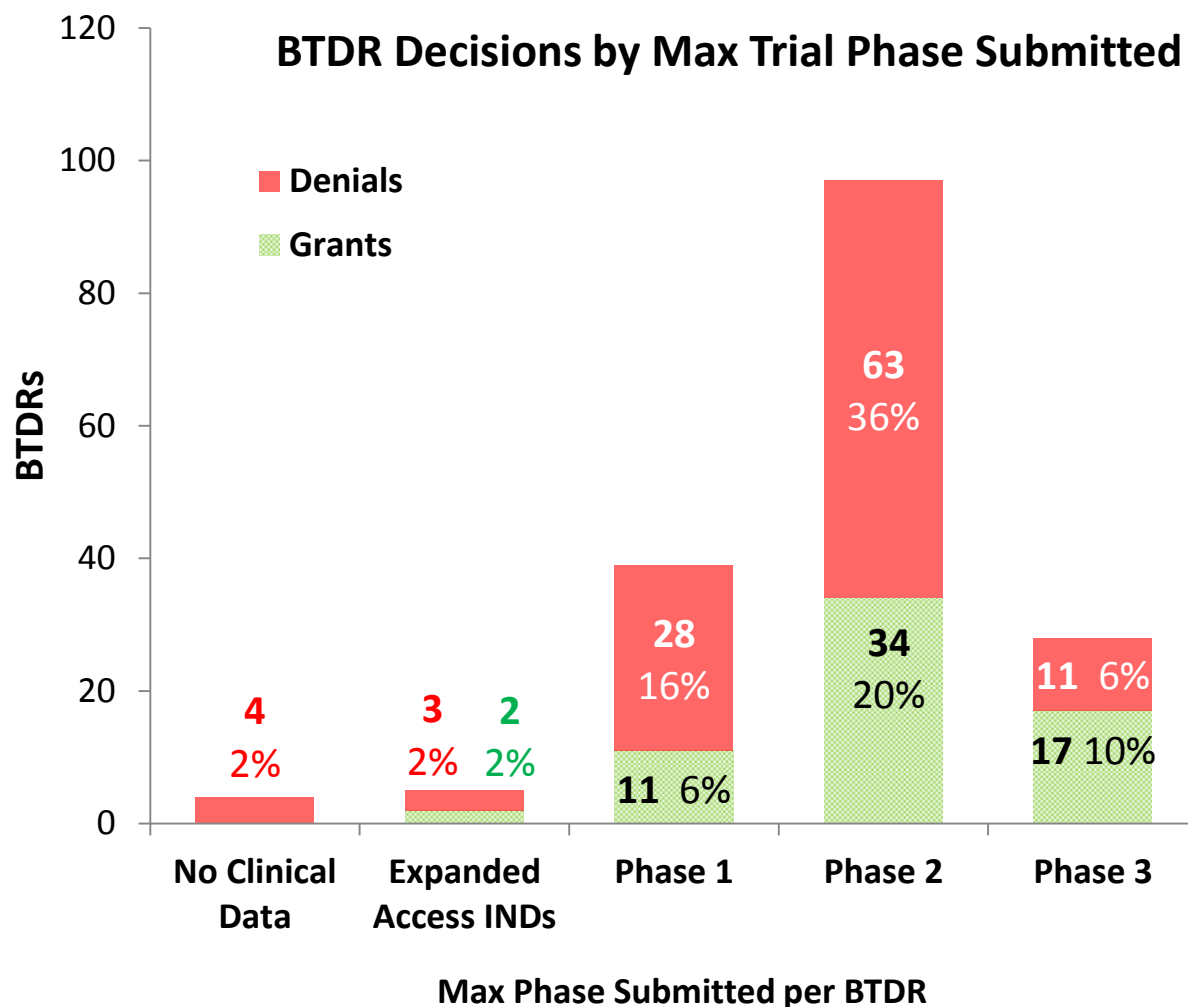
Most BTDRs submitted data from a single trial

- Among grants, 33% had data from 2 or more trials
 - Includes 10 submissions with data from 3+ trials
- Among denials, 21% had data from 2 or more trials
 - 4 submissions submitted no human clinical data
- High quality data from one trial tends to be better than lower quality data from many trials

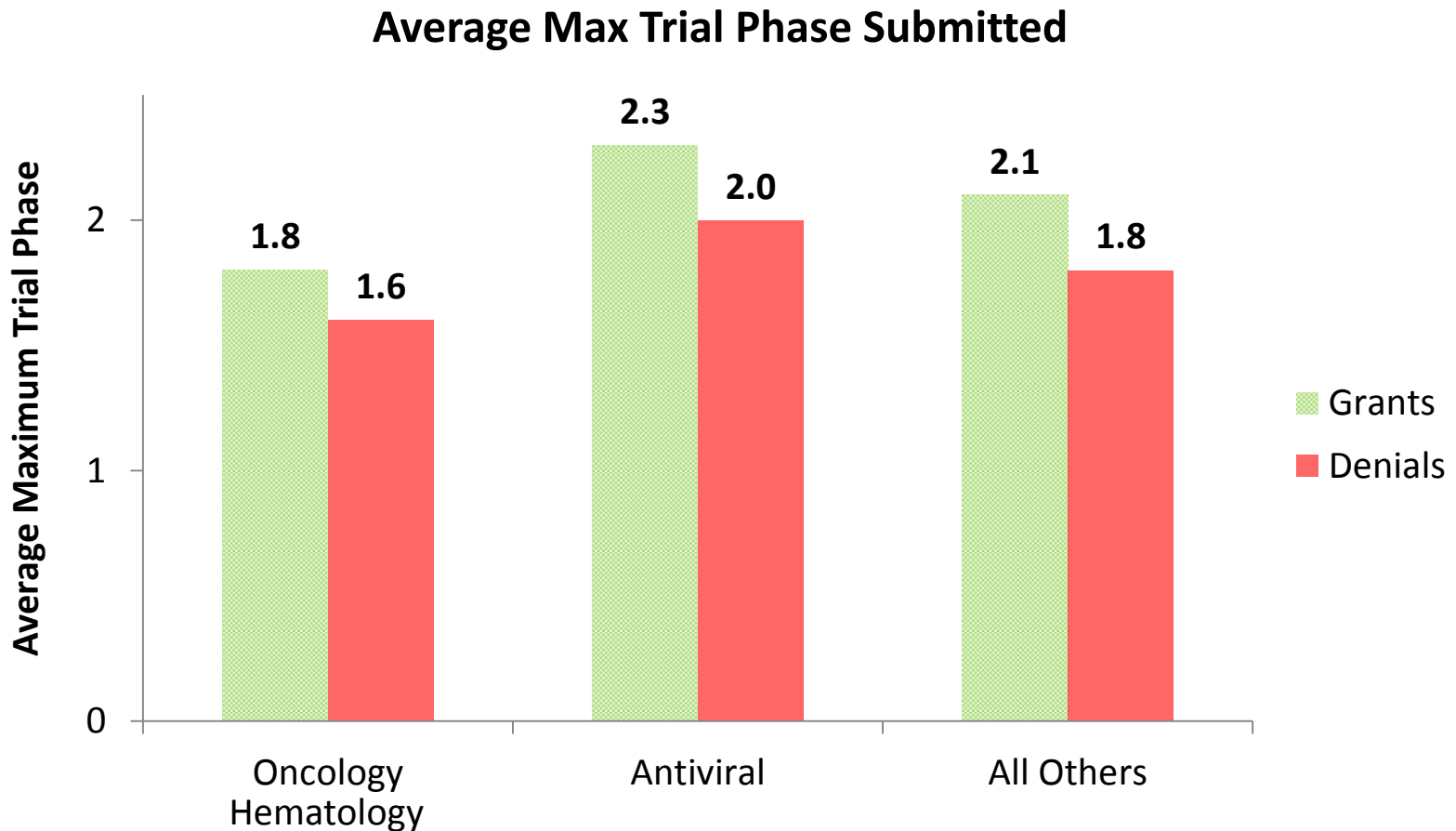


Most BTDR decisions were based on data from phase 1 and phase 2 trials

- Most sponsors are adhering to the expedited programs' guidance and submitting at phase 2 or earlier
- Data from phase 3 trials not common in either grants, denials
- Two grants based only on data from expanded access INDs – clinical evidence not from a trial

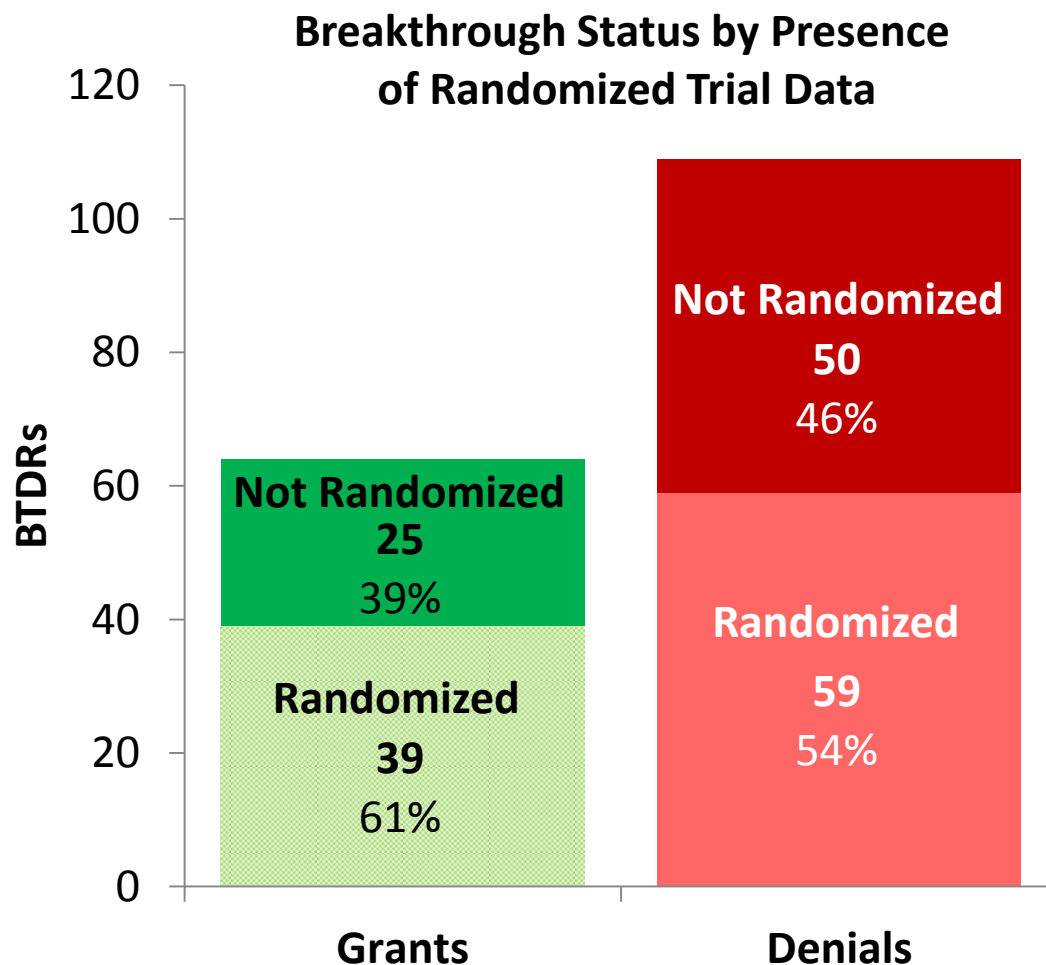


Oncology and hematology BTDRs were submitted earlier in drug development than other requests



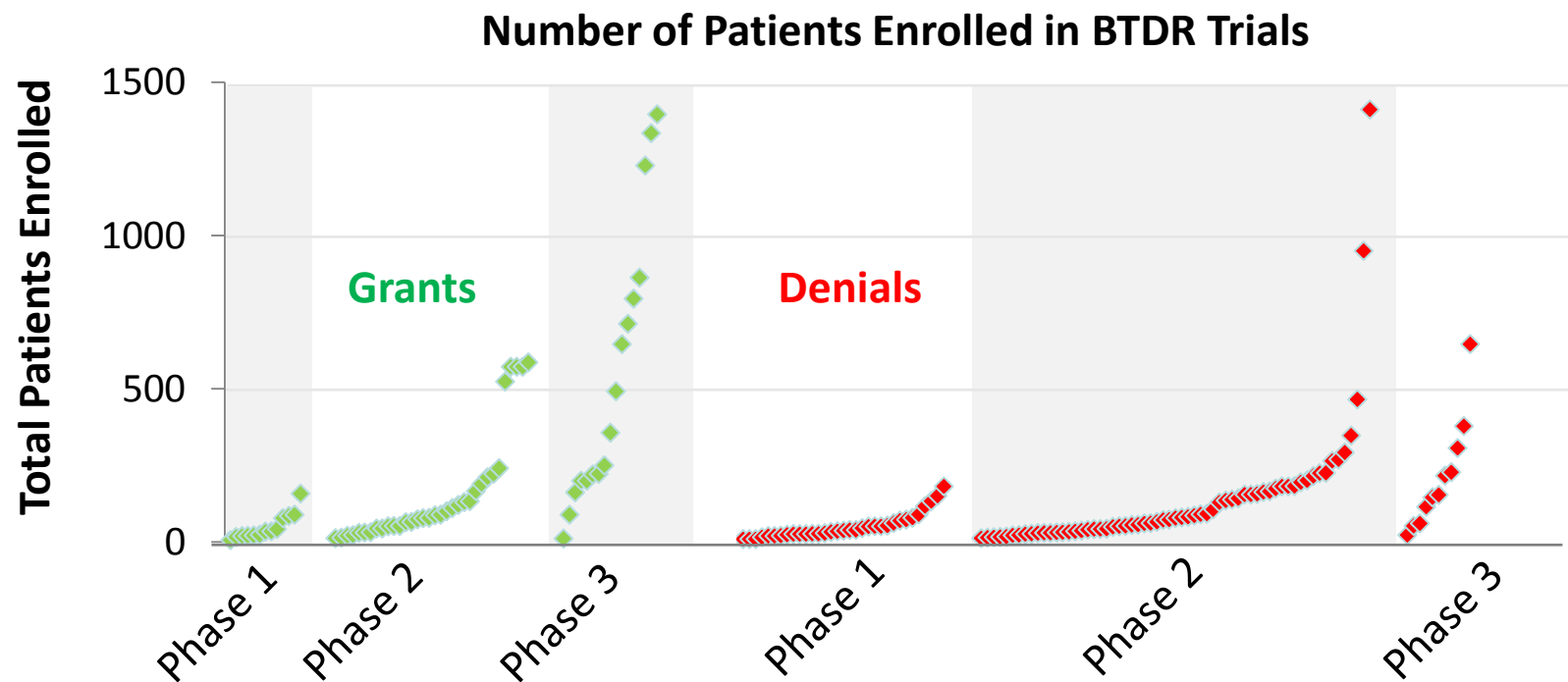
Randomized trials were not always necessary to gain breakthrough status

- 39% of grants did not submit data from randomized trials compared to 46% of denials
- Trial designs varied widely – successful requests provided scientific/medical justification



Appropriate trial enrollment depended on the specific indication and drug

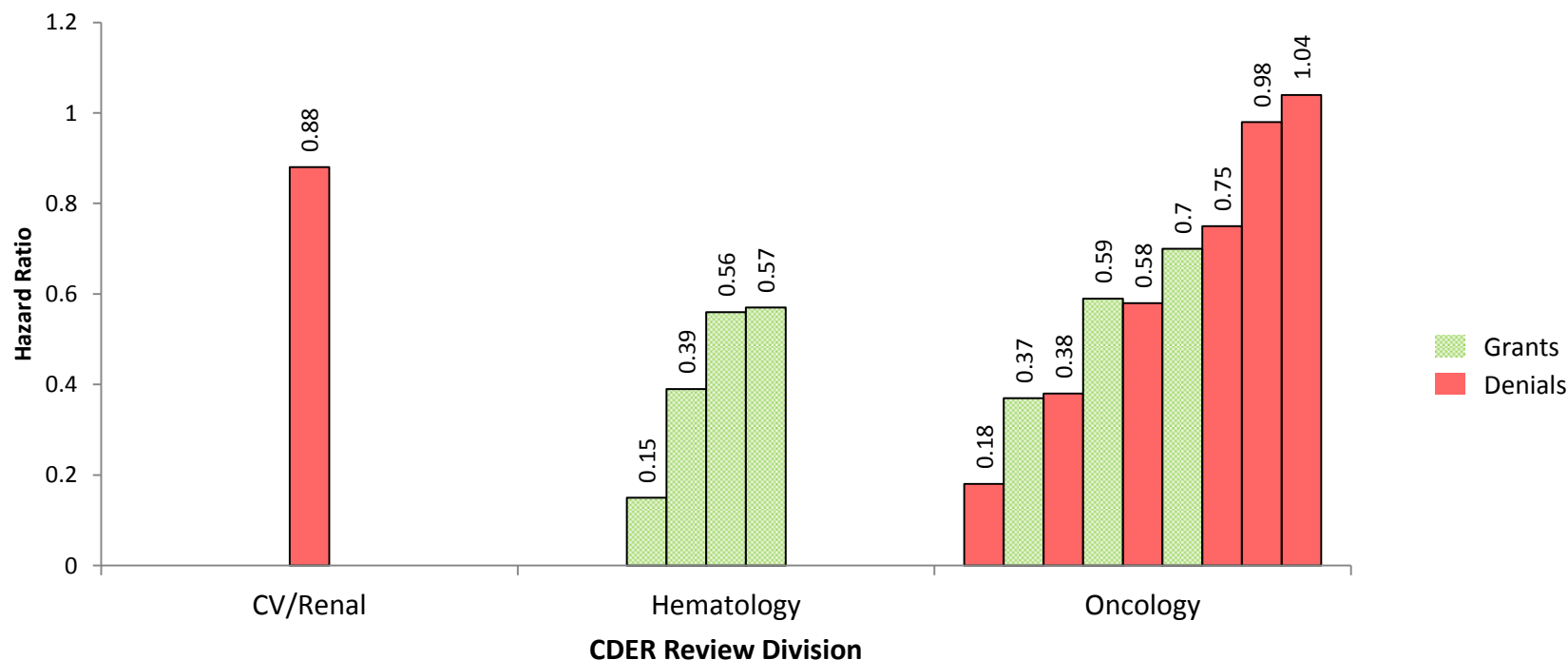
- BT status has been granted with <10 studied patients; denied with >1000 patients enrolled



Hazard ratios averaged .48 for grants and .68 for denials

- Hazard ratios provide a standardized method of comparing treatment effects for randomized trials across divisions/therapeutic areas. But all but one of the hazard ratios noted by evaluators were for oncology and hematology BTDRs
- On average, hazard ratios for grants were more favorable than those of denials; however, no clear threshold is apparent, indicating other factors may play a significant role in BTDR decision

Primary Endpoint Hazard Ratios from BTDRs ¹



¹ Hazard ratios only apply to BTDRs with randomized trials; hazard ratios were included in review materials for 14 BTDRs

III. OHOP Treatment Effect Case Study: What Does an OHOP (Office of Hematology & Oncology Products) BT Designation Grant Look Like by the Numbers?

Examined treatment effect information for OHOP grants to better understand “substantial improvement”¹

- Endpoints and available therapy comparators varied too much across divisions to directly compare treatment effects for all BTDRs
- Instead examined treatment effect data for a comparable subset of OHOP grants
- Analysis strictly compares treatment effects by primary endpoint results and ignores the nuances of each grant: seriousness of condition, trial characteristics, effect duration, etc.....
- Analysis is meant to be representative, not definitive

¹Case study assumptions can be found in the appendix

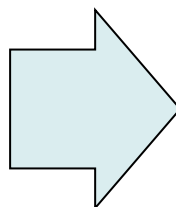
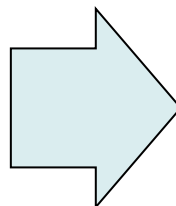
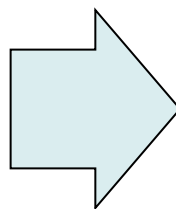
OHOP grants were grouped into 3 categories based on availability of other therapies and primary endpoint

OHOP Grant Grouping

Drugs submitted with randomized trial information and hazard ratios, *regardless of whether available therapies exist for same indication*
(n=7)

Drugs submitted without hazard ratios *for which there are available therapies for same indication*
(n=8)

Drugs submitted without hazard ratios *for which there are no available therapies for same indication*
(n=12)



Treatment Effect Information Gathered

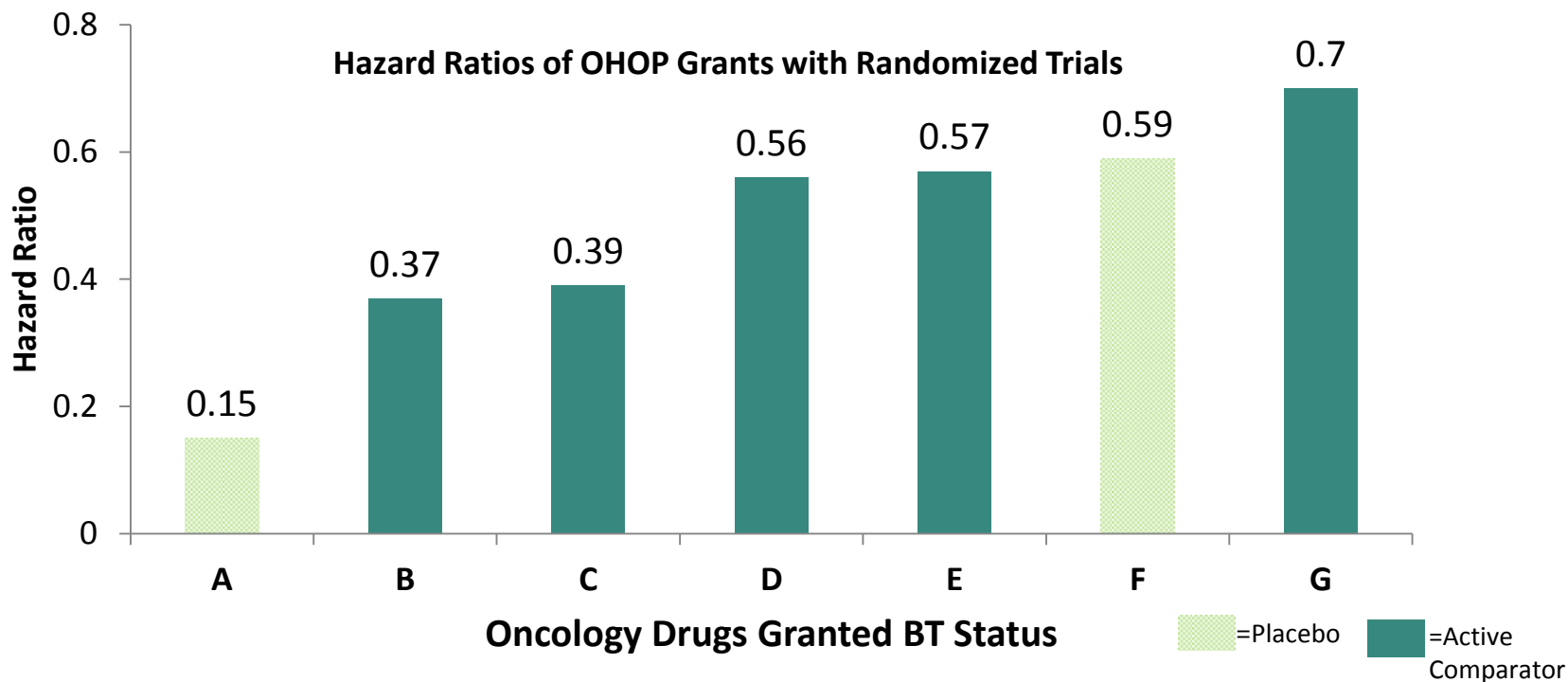
Hazard ratio for primary endpoint
*noted availability of other therapies, improved safety profiles, and type of control

Difference between primary endpoint value and value for most effective available therapy
*noted improved safety profiles

Primary endpoint value (Objective Response Rate)

OHOP grants with randomized trials that also supplied a hazard ratio had an average HR of .48¹

- Of the two drugs with the least impressive treatment effects, one had an improved safety profile over available therapies (drug F) and the other had no available therapy (drug G). Both drugs also used overall survival (OS) as the endpoint.
- At this time, there is no noticeable trend by control type (i.e., active comparator or placebo).

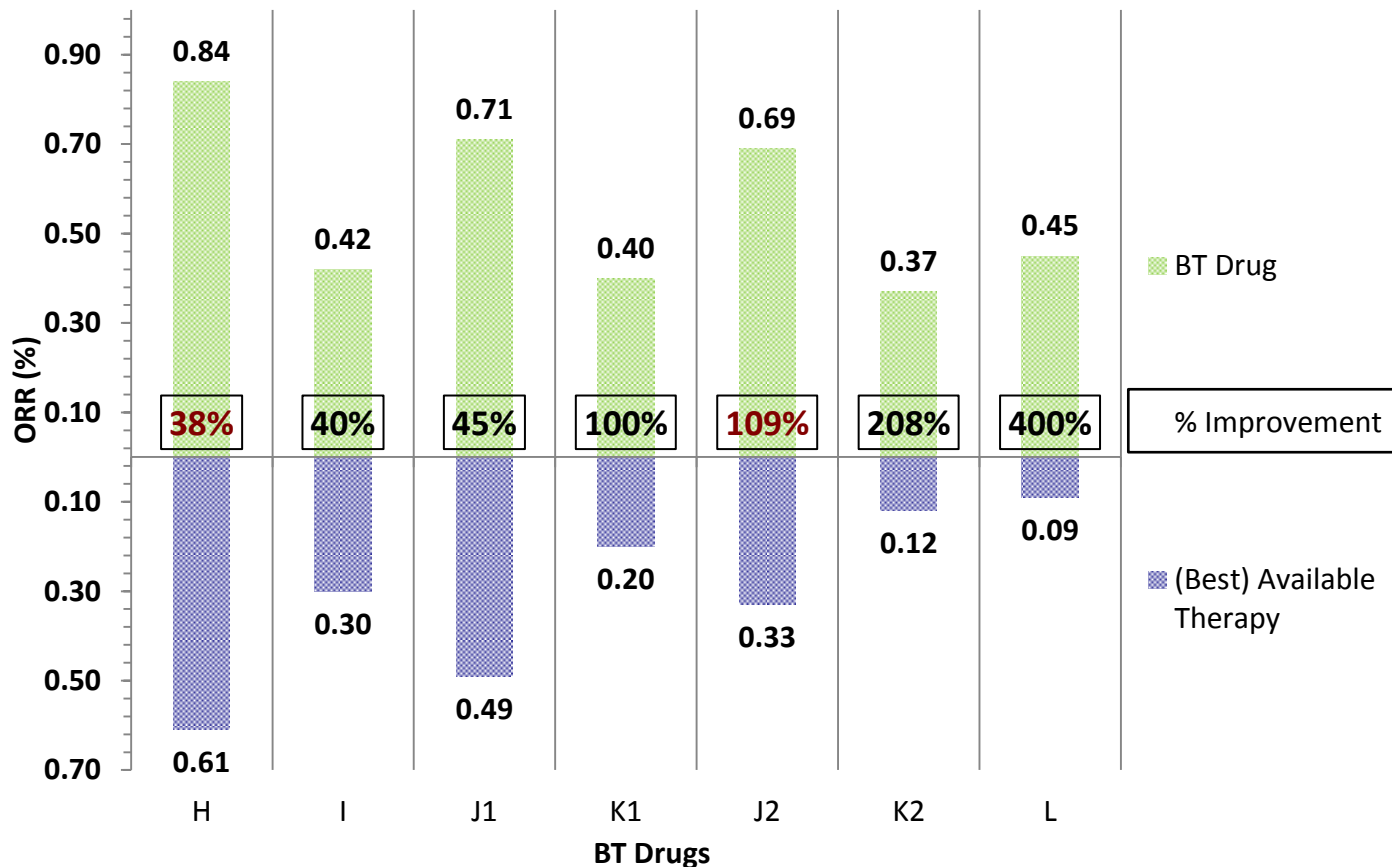


¹Endpoints included progression-free survival (PFS), event-free survival (EFS) and OS; All but one drug were for indications with available therapies; One drug had an improved safety profile over available therapy

Improvement in ORR¹ over best available therapy ranged from 38% to 400% for OHOP grants

- Average ORR = 55%
Median ORR = 45%
Range = 37-84%
- Not surprisingly, two largest improvements were over least effective available therapies
- 2 BT drugs in this category had improved safety profiles over available therapies (red).
- Note that one drug with improved safety is not pictured here, because BT drug did not use ORR. (Percent improvement for this drug was 75%.)

ORRs of OHOP Grants and Best Available Therapies for Therapeutic Area²

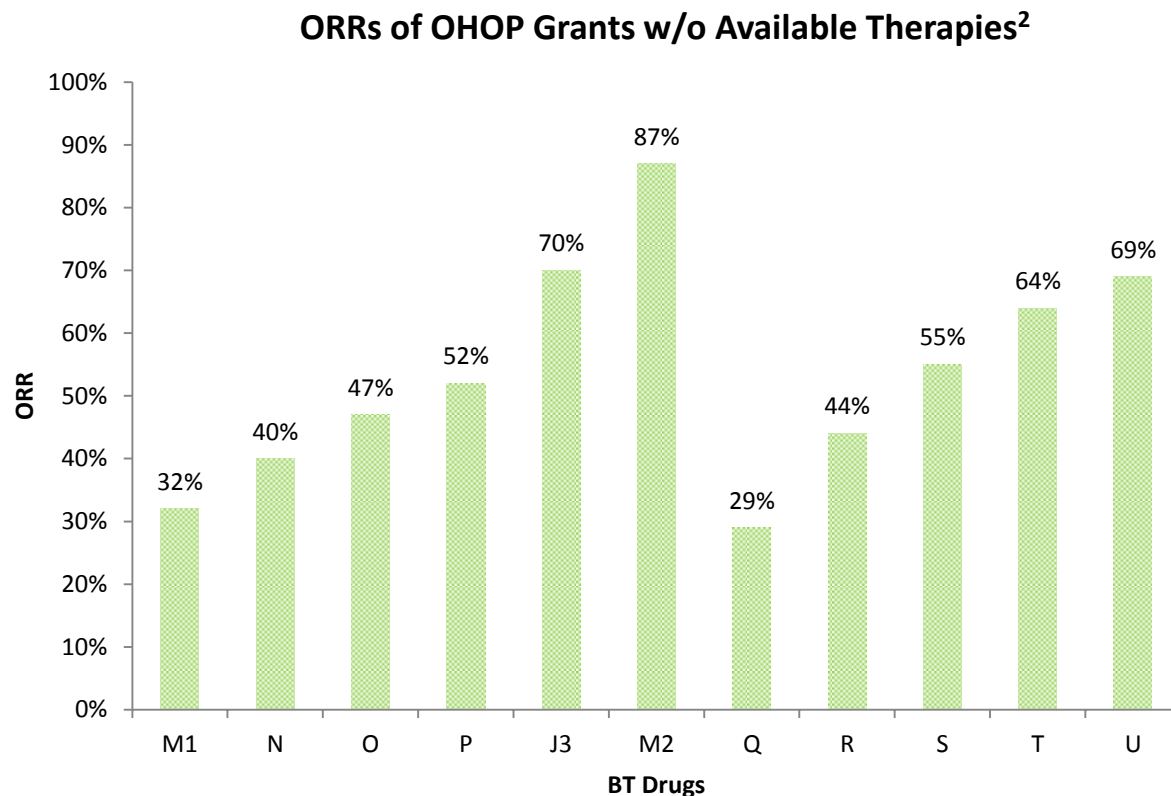


¹ORR = Objective Response Rate

²Numbers following a letter indicate multiple indications for the same drug

ORRs¹ for OHOP grants without available therapies ranged from 29% to 87%

- Average ORR = 54%
Median ORR = 52%
- Drugs Q-U are various indications for non-small cell lung cancer (NSCLC)



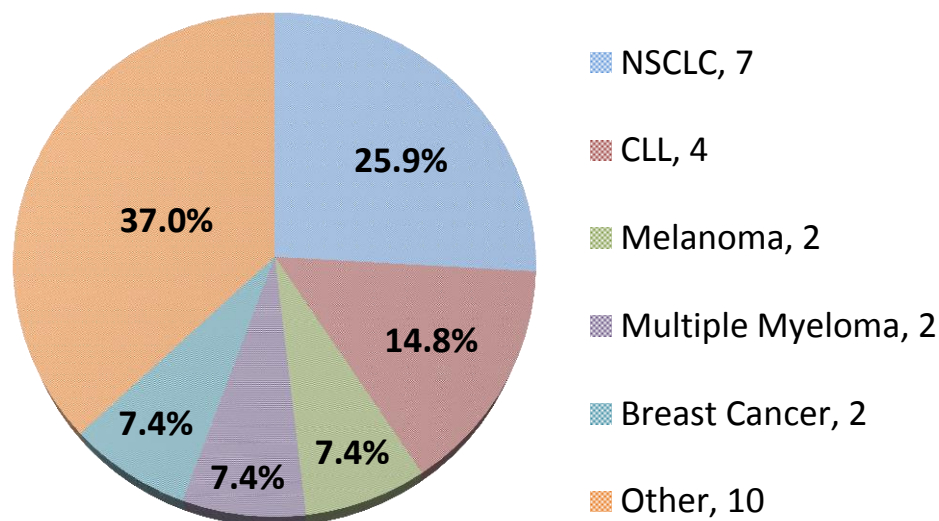
¹ORR = Objective Response Rate

² 1 drug in this category was left out of this analysis because the endpoint was not ORR. Numbers following a letter indicate multiple indications for the same drug

37% of OHOP grants were “unique” indications

- Various non-small cell lung cancer (NSCLC) indications make up more than a quarter of all OHOP grants
- Combined, various indications for NSCLC and chronic lymphocytic leukemia (CLL) make up more than 40% of all OHOP grants
- Various leukemia and lymphoma indications (including CLL) make up 30% of all OHOP grants

% of Total OHOP Grants by Therapeutic Area

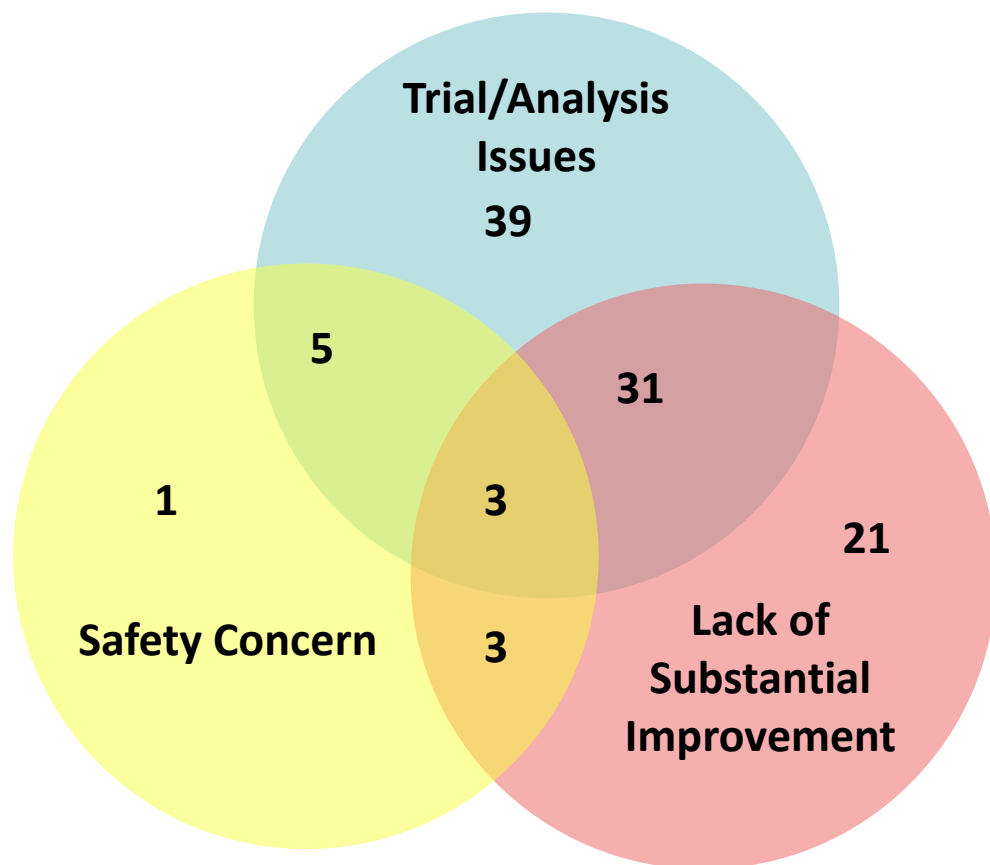


IV. Denial and Withdrawal Rationales

Analysis:

Why are BTDRs Denied or Withdrawn?

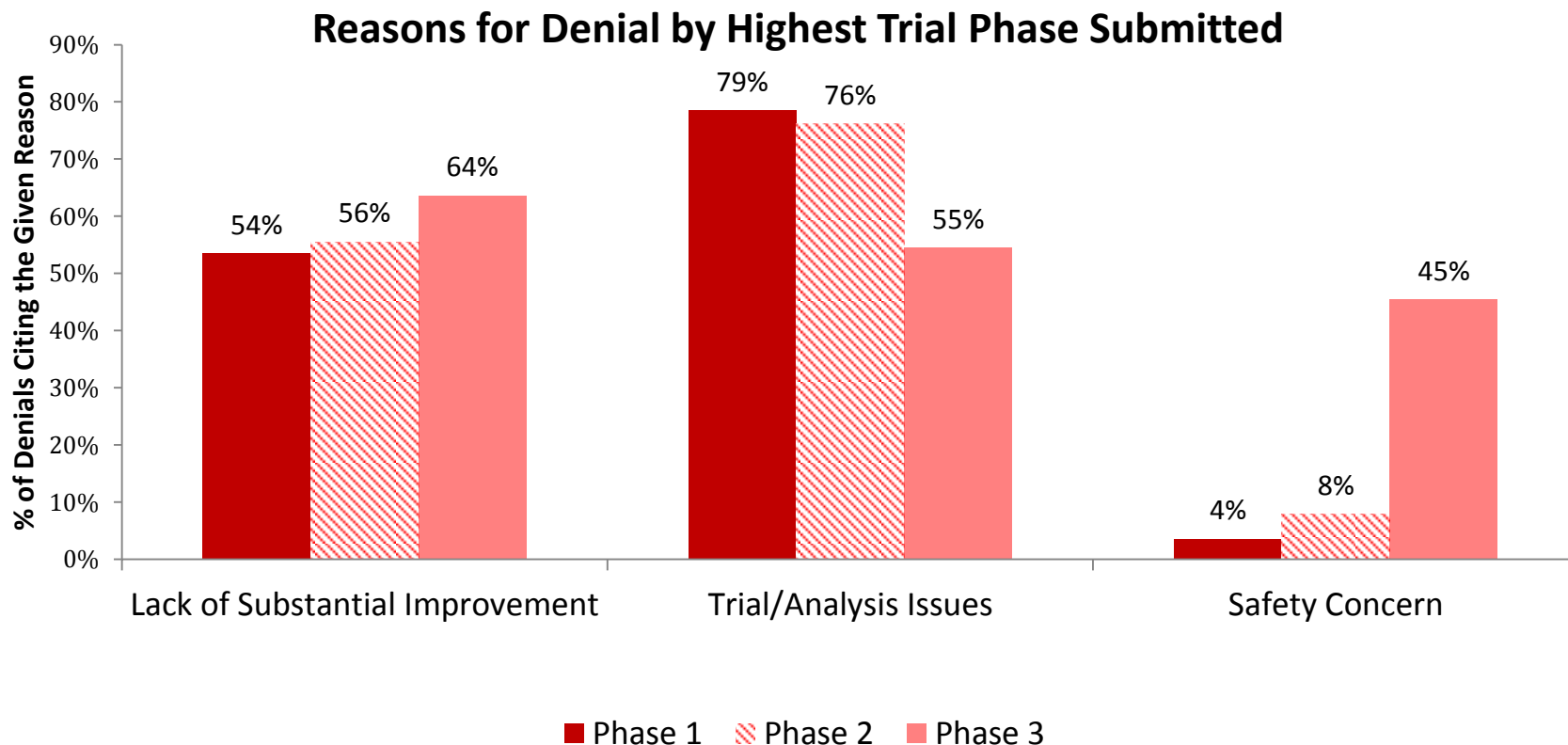
Reliability of clinical evidence was a more common rationale for BTDR denial than lack of substantial improvement



Denials N=109	
Reasons for Denial ¹	
Trial/analysis issues	78 (72%)
Trial design issues	45 (41%)
Sample issues	39 (36%)
Endpoint issues	29 (27%)
Results too preliminary	19 (17%)
Flawed post-hoc analysis	17 (16%)
Lack of substantial improvement	58 (53%)
Lack of data	18 (17%)
No clinical data	4 (4%)
Incomplete data	14 (13%)
Safety concern	12 (11%)
Miscellaneous	14 (13%)
Not serious condition	2 (2%)
Other	12 (11%)

¹Totals exceed 100% as many denials cited multiple reasons for denial. Definitions of each grouping can be found in the appendix.

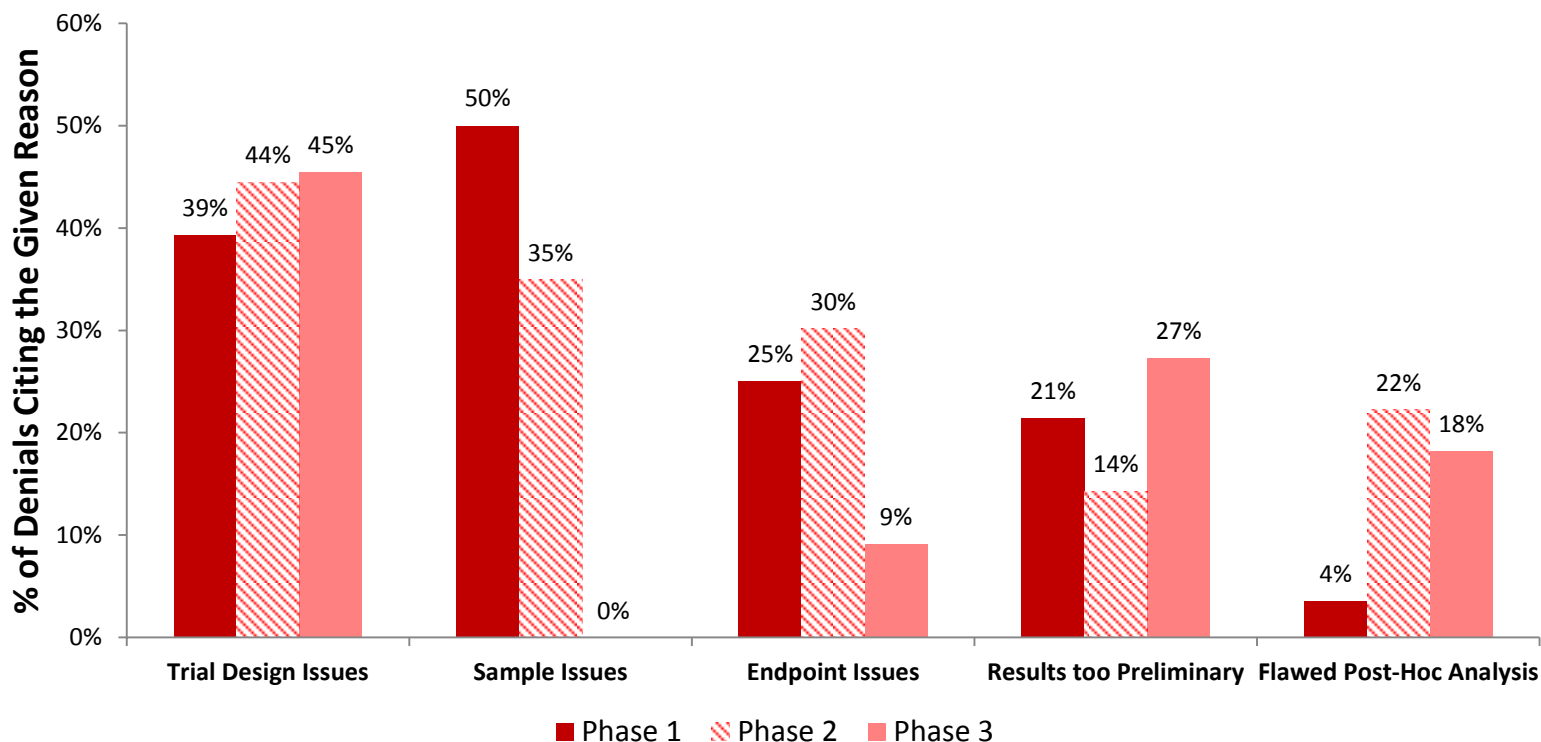
Efficacy and safety became bigger concerns as maximum trial phase submitted¹ increased



¹28 denials had at most Phase 1 data; 63 denials had at most Phase 2 data; 11 denials had at most Phase 3 data; 3 denials used expanded access IND data, 4 did not submit any human data

There was no discernable pattern of trial and denial issues by highest phase submitted¹

Trial/Analysis Issues by Highest Phase Submitted

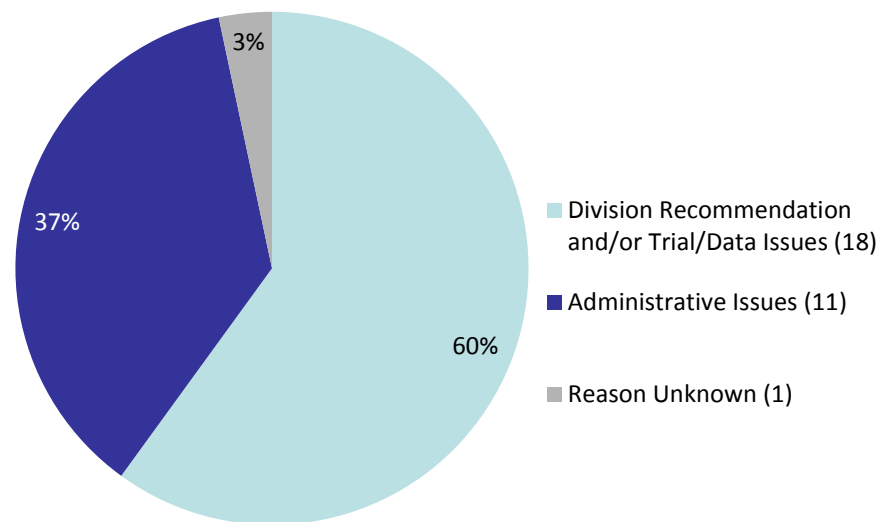


¹28 denials had at most Phase 1 data; 63 denials had at most Phase 2 data; 11 denials had at most Phase 3 data; 3 denials used expanded access IND data, 4 did not submit any human data

Many BTDRs were withdrawn¹ prior to CDER granting or denying the request

- Many sponsors chose to withdraw their applications rather than risk a denial
- 3 WDs were resubmitted and decided upon by the end of 2014
- 40% were withdrawn by private sponsors (who submitted 26% of total BTDRs)
- 80% of withdrawals were for oncology, hematology and antiviral drugs (consisting of 60% of total BTDRs)

BTDR Withdrawal Rationales²



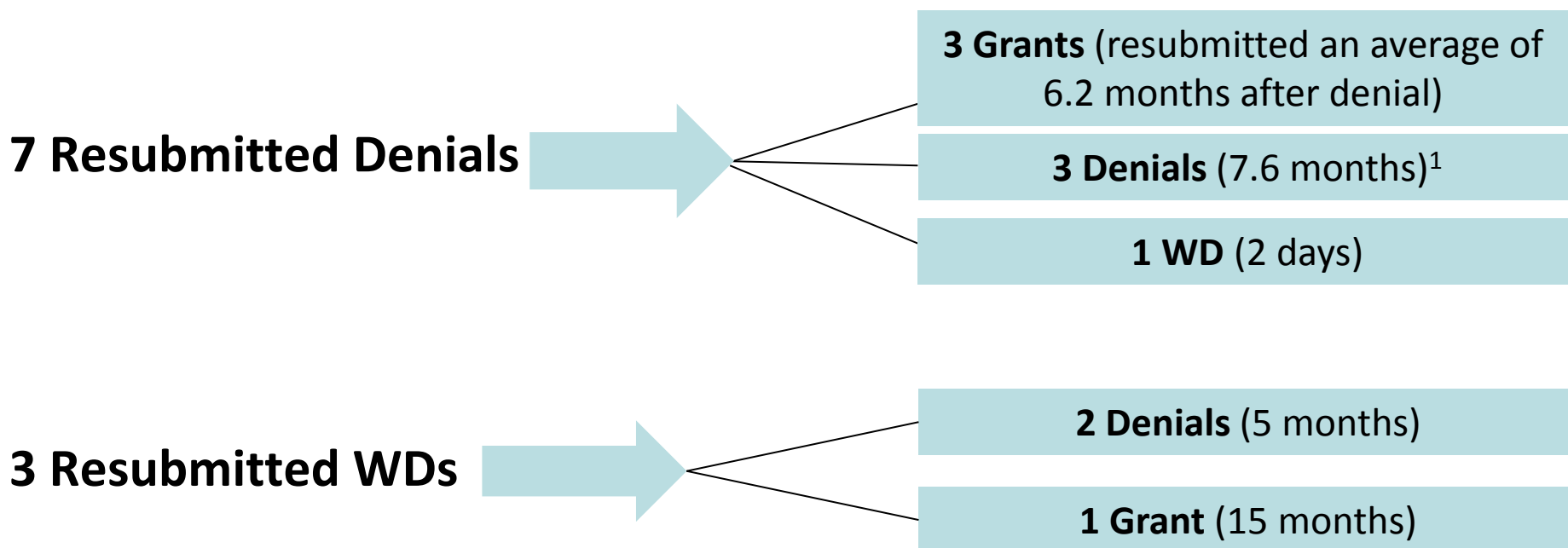
¹ 2 BTDRs were withdrawn after receiving BT designation; they were excluded from this withdrawal analysis .

² "Administrative issues" include those BTDRs that were withdrawn because they were submitted at the pre-IND phase, submitted under an alternate IND instead, submitted to Fast Track instead or were withdrawn to avoid a clinical hold. "Division recommendation/trial/data issues" includes incidences where sponsors withdrew their requests after conversations with divisions led them to think they may be denied. It also includes incidences where sponsors chose to withdraw of their own accord due to data or trial issues, such as after the failure of a Phase 3 trial.

³ Sponsors that did not have sponsor data available in the FDA DUNS database were categorized as private sponsors .

Many sponsors submitted new requests for denied or withdrawn BTDRs

10 Resubmissions: 60% for oncology and hematology drugs, 20% for antivirals, 20% for other drug types



¹Times reflect average time to resubmission

V. Conclusions: What Have We Learned After Two-and-a- Half Years of the Program?

There is no one-size-fits-all characterization of a BT drug nor a definitive threshold for substantial improvement

- BTDR decisions are complex and while there is no one-size-fits-all characterization of a BT drug, some preliminary patterns were observed in BT program and decision characteristics
- The reliability and persuasiveness of clinical evidence is critical to making the BTDR decision.
- There is wide variation by therapeutic area in trial characteristics, patient populations and available therapies. Thus, any characterization of a substantial improvement threshold may be best approximated by therapeutic area. However, the small number of BT grants and denials in each area thus far make it difficult to do so this early in the program.

Program and decision characteristics:

- BT is a popular program with many strong candidates, particularly in the oncology, hematology and antiviral classes.
- Most successful BTDRs were from large, US sponsors with regulatory experience.
- No pattern was identified in terms of whether a drug had an available therapy or orphan and/or rare status, but trends were observed by therapeutic area.
- BTDRs for indications that had prognostic biomarkers had a higher proportion of grants.
- BT grants submitted more trials on average and these trials were more likely to be randomized.
- Most BTDR decisions were based on phase 1 and phase 2 trial data.
- There was no discernable pattern to trial enrollment; appropriate enrollment depended on the specific indication.
- Trial and analysis issues followed by lack of substantial improvement were the top denial rationales.
- Most withdrawals occurred for administrative reasons or because the division indicated to the sponsor the BTDR would be denied.

VI. APPENDICES



Definitions

- **Available therapy:** Other therapies that are approved in the US for and/or are the US standard-of-care for the BTDR indication.
- **Number of trials:** Number of clinical trials submitted as evidence relevant to BT indication and decision.
- **Orphan and/or rare:** IND is specified as orphan and/or rare at the time of data collection.
“Orphan” consists of drugs who applied for and received orphan designation from the FDA.
“Rare” includes those indications categorized by the FDA as rare (affecting <200,000 people in the US).
- **Prognostic biomarker:** Biological characteristic that is objectively measured and evaluated as an indicator of pathologic processes that can categorize patients by degree of risk for disease occurrence or progression of a specific aspect of a disease.
- **Sponsor size :** Number of employees the sponsor (or parent if applicable) has the year the BTDR was submitted:
 - Small: <250 (public)
 - Medium: 250-15,000 (public)
 - Large: >15,000 (public)
 - Private: Privately held (any size)
- **Treatment effect:** Endpoint value or percent improvement over best available therapy.
- **U.S. regulatory experience:** Parent company of sponsor has a drug listed in the Orange Book.

Definitions cont.

- **Rationale for Denial:**

- Endpoint issues: Lack of a defined endpoint, faulty/flawed endpoint, or primary endpoint not supported or predictive of clinical benefit. (Note that failing a primary endpoint does not constitute this rationale.)
- Flawed post hoc analysis: Flawed post hoc analysis.
- Incomplete data: Essential data omitted from BTDR.
- Lack of substantial improvement: Drug does not seem to constitute a significant improvement over available therapies (or standard treatment).
- Misc./other: Any other denial rationale.
- No clinical data: No clinical data submitted.
- Not serious condition: Indication not serious enough to warrant BT.
- Results too preliminary: Trial results submitted in BTDR garnered from too early in the study phase.
- Safety concern: Specific safety concern noted.
- Sample issues: Sample size too small given the indication or sample is not representative of the patient population.
- Trial design issues: Treatment effect not isolated, inappropriately uncontrolled or unblinded trial, etc.

OHOP Analysis approach decisions and assumptions

- Focused on the treatment effect for each OHOP grant related to the specific BT-designated indication
- Because the expedited program guidance does not account for unapproved therapy comparisons (drugs in pipeline, off-label use, etc.) they were not taken into account in this analysis
- Treatment effects with Objective Response Rate (ORR) endpoints do not include the split between complete response (CR) and partial response (PR) because that information was not always known
- Used confirmed ORRs in the analysis
- Where multiple available therapies existed for the same indication as the BT-designated drug, the drug with the highest/best treatment effect and the same endpoint as the OHOP grant was used
- Where multiple data points for OHOP grants and available therapies existed, worked with an OHOP Medical Officer (OND) to identify the ones most relevant to this analysis
- Anonymized drugs using letters and numbers: Where one drug (e.g., drug A) was granted BT for more than one indication, numbers follow the same letter (e.g., A1, A2, A3)

Breakthrough Therapy Designation: Exploring the Qualifying Criteria

Park Hyatt Hotel • Washington, DC
Friday, April 24, 2015



Case Study for Breakthrough Therapy Designation: Keytruda[®] (pembrolizumab, MK-3475) for treatment of patients with unresectable or metastatic melanoma

Sponsor: Merck Sharp and Dohme Corporation

Jennie Chang, Pharm.D., Clinical Reviewer
Marc Theoret, MD, Team Leader
Melanoma and Sarcoma Team
Office of Hematology and Oncology Products
Center for Drugs and Evaluation Research
United States Food and Drug Administration
April 24, 2015

Metastatic Melanoma

- Metastatic Melanoma is a Serious Disease With 5-year Survival ~15%
- FDA-approved Therapies for Unresectable or Metastatic Melanoma:

Unselected patients

	<u>ORR</u>
Interleukin 2	16%
Dacarbazine	5-20%
Ipilimumab*	11%

BRAF V600 mutation

	<u>ORR</u>
Trametinib (T)	22%
Dabrafenib (D)	52%
D + T Combo	76%
Vemurafenib*	48%

*** Demonstrated OS improvement**

Pembrolizumab (MK-3475)

- **Proposed Indications:**

- Treatment of unresectable or metastatic melanoma that is refractory to ipilimumab treatment
- Treatment of unresectable or metastatic melanoma in patients who have not received prior ipilimumab therapy.

- **Mechanism of Action:**

- Human monoclonal IgG4 antibody that blocks interaction between PD-1 and ligands, PD-L1 and PD-L2.
- Blockade enhances functional activity of target lymphocytes to facilitate tumor regression and immune rejection.
- PD-1 pathway: major immune control switch that may be engaged by ligands expression in tumor microenvironment to overcome active anti-tumor specific T-cell immune surveillance.

P001 Study Design

- IND submitted: December 9, 2010
- First patient allocated to treatment: April 27, 2011
- Study P001: Part B (melanoma cohort)
- Objective:
 - Safety and anti-tumor activity of pembrolizumab in locally advanced unresectable and metastatic melanoma.
- Patient population: ipilimumab-naïve and ipilimumab-treated
 - Includes BRAF mutant and wildtype, BRAF mutant may be treated with BRAF or MEK inhibitor
- Two dose levels: 2 mg/kg and 10 mg/kg

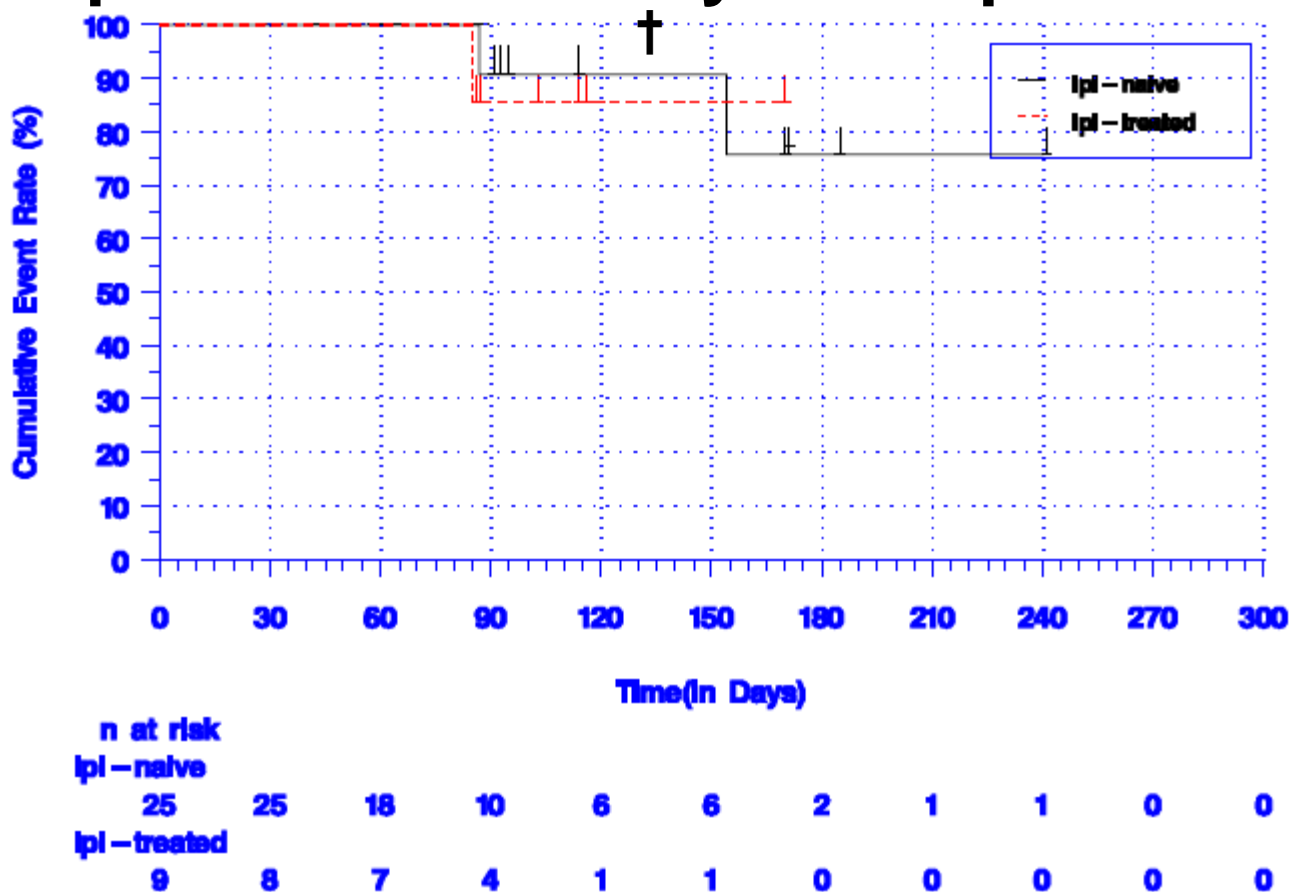
Rationale for Breakthrough Designation

	Objective Response (N, 95% CI)	Complete Response (N, 95% CI)	Duration of Response (days) Median (range)
All melanoma* N=85	40% (34; 29%-51%)	3.5% (3; 0.7% - 10%)	Not reached (28-240+)
Ipi-naïve N=58	43.1% (25; 30%-57%)	3.4% (2; 0.4% - 11.9%)	Not reached (30-240+)
Ipi-treated N=27	33.3% (9; 16%-54%)	3.7% (1; 0.1% - 19%)	Not reached (28-169+)

† Based on independent centralized review using RECIST 1.1 as of 12/3/2012.

* All patients dosed at 10 mg/kg.

Kaplan-Meier Estimates of Confirmed Response Duration by Prior Ipilimumab



† Based on independent centralized review.

Safety

- Common adverse events, regardless of attribution: fatigue, nausea, rash, diarrhea, cough, pruritus (itch), arthralgia (joint pain), and headache
- Grade 3 or 4 AEs, regardless of attribution: 27%
- Incidence of immune-related adverse events as reported by the investigators: 16%

Safety (cont.)

- 7 immune-related Grade 3-5 AEs:
 - interstitial nephritis, pleuritic pain, pancytopenia, pneumonia/pneumonitis, abdominal pain/vomiting, hyperthyroidism, and hypothyroidism
 - Improved or resolved with supportive care and treatment with corticosteroids
 - Two Grade 5 (fatal) AEs
 - Pneumonia/pneumonitis
 - Abdominal pain/vomiting

Division's Recommendations

- Grant Breakthrough Therapy Designation on January 17, 2013, based on the following:
 - MK-3475 is intended to treat a serious disease.
 - Preliminary evidence from Study P001 indicated that MK-3475 may demonstrate a substantial improvement over existing therapies for melanoma based on high rate of responses (33-43%) with prolonged response durations (4-8+ months) in ipilimumab-naïve and in ipilimumab-treated patients.

Breakthrough Therapy Designation for AP26113 (IND: 110935)

Case review of Brigatinib (AP26113):

Indicated for the treatment of patients with anaplastic lymphoma kinase positive (ALK+) non-small cell lung cancer (NSCLC) that is resistant to crizotinib

Diko Kazandjian, MD: Medical Officer

Gideon Blumenthal, MD: Team Leader

Division of Oncology Products 2/OHOP/OND/CDER/FDA

Sponsor: Daniel M. Bollag, Ph.D: Senior VP, Regulatory Affairs & Quality; Ariad Pharmaceuticals, Inc.

Background on NSCLC

- ❖ Standard platinum containing doublets are the mainstay of first-line treatment for advanced disease in an unselected population

ORR	PFS	OS
~30%	~5 months	~10 months

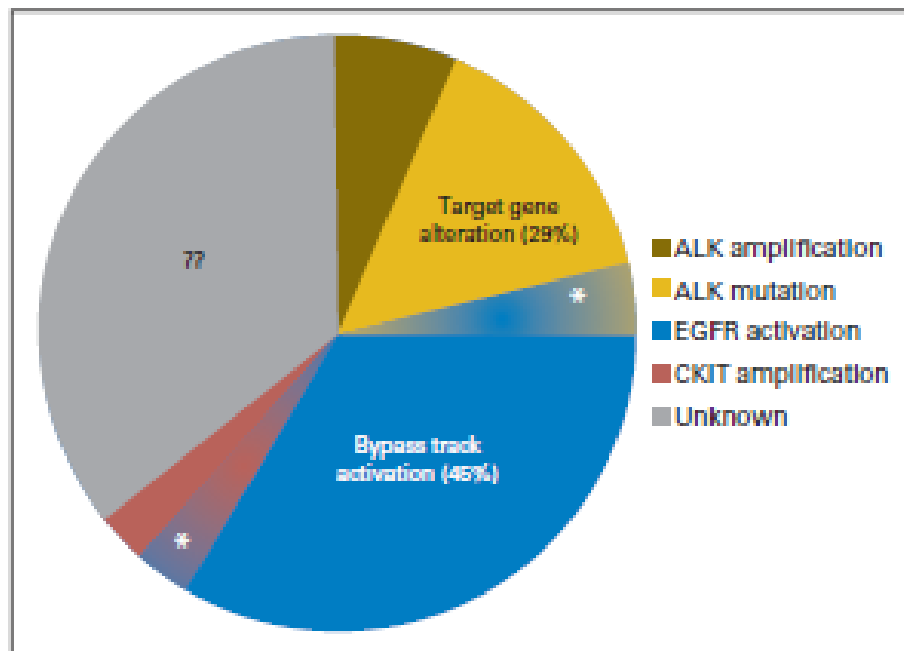
- ❖ Docetaxel, erlotinib, pemetrexed, & ramucirumab are approved for unselected metastatic 2nd line treatment of NSCLC

Drug	ORR	Median PFS	Median OS
Pemetrexed	9.1%	2.9 months	7.9 months
Docetaxel	8.8%	2.9 months	8.3 months

ALK positive NSCLC

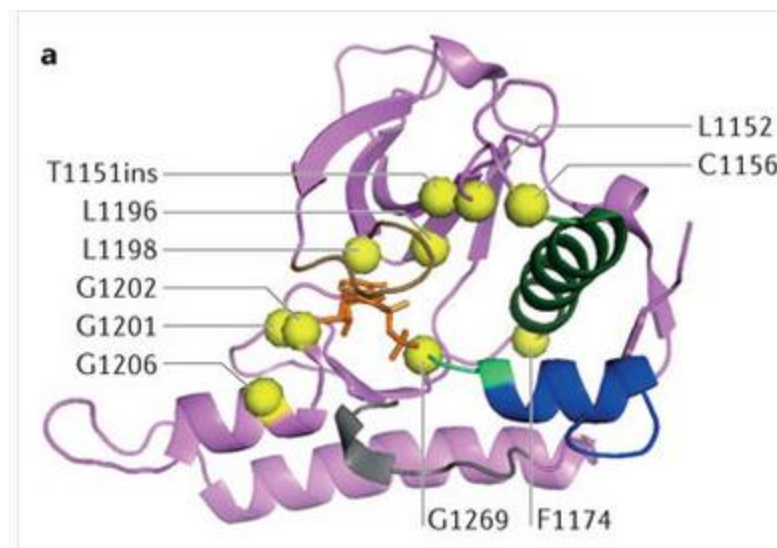
- ALK alterations are present in about 5% of NSCLC patients
- SoC is to test for EGFR and ALK alterations
- 1st line treatment: Crizotinib is indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test (Regular Approval).
- 2nd line treatment: Recent Accelerated Approval of 2nd generation ceritinib (4/2014) for the treatment of patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib.

Crizotinib Resistance



Shaw & Engelman, J Clin Oncol, 2013

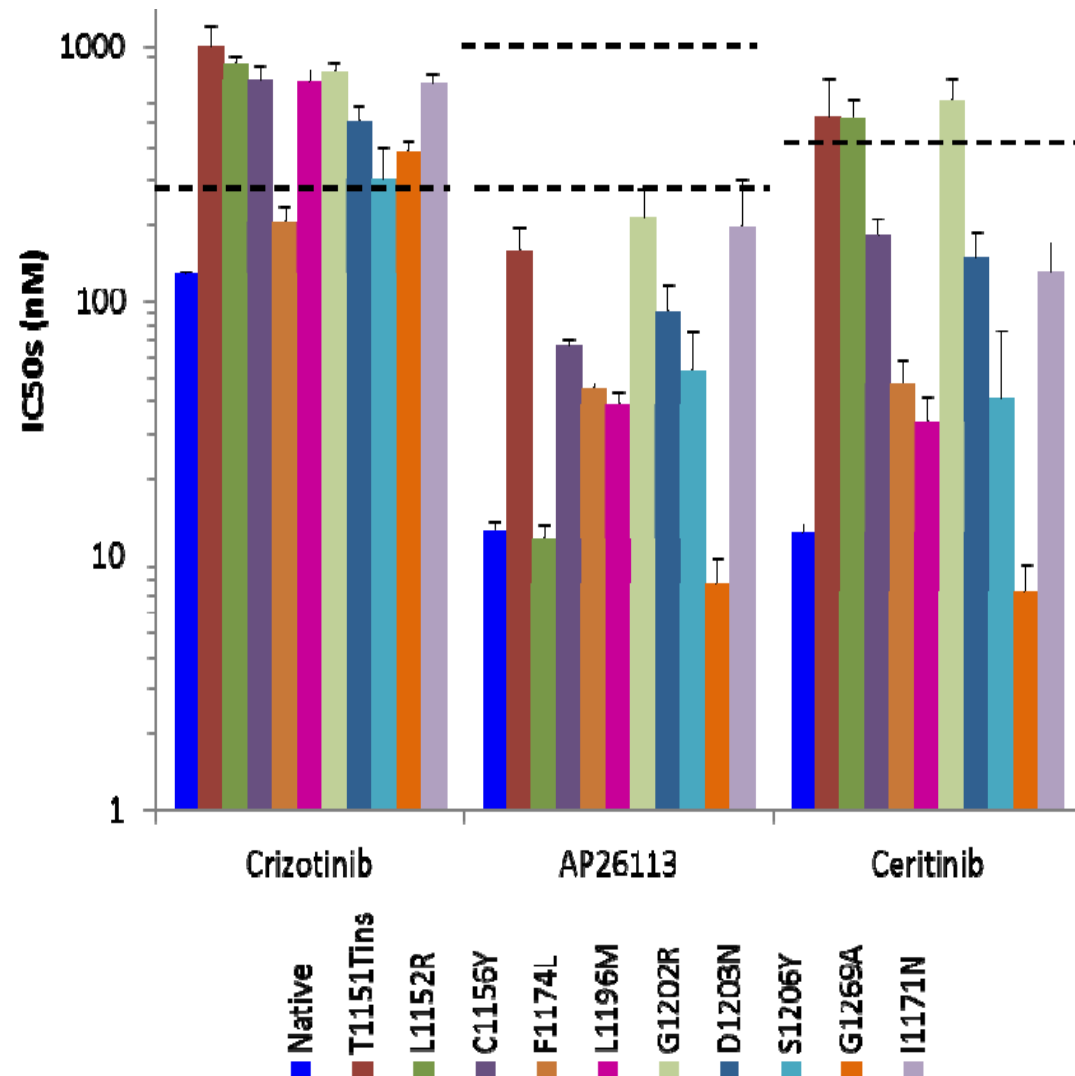
ALK mutations: Many gate keepers



Hallberg & Palmer, Nat Rev Cancer, 2013

AP26113 Proposed Indication

- For the treatment of patients with ALK-positive metastatic NSCLC that is resistant or intolerant to crizotinib.
- Inhibits activated forms of ALK, including L1196M.



Phase 1/2 study – ongoing

- Phase 1: Dose Finding
- Phase 2: 5 Expansion Cohorts/Eligibility
 1. ALK+ NSCLC, prior TKI naïve
 - History of ALK rearrangement by FISH
 - No ALK inhibitor therapy
 2. ALK+ NSCLC, resistant to crizotinib
 - History of ALK rearrangement by FISH
 - Crizotinib Resistance and no other prior ALK inhibitor therapy
 - 3-4. Other Indications
 5. ALK+ NSCLC patients with active, measurable brain mets

Development Plan

Accelerated Approval:

Indication to target previous crizotinib treated patients based on ORR from two studies:

1. Current ongoing Phase 1/2 study
2. Uncontrolled randomized phase 2 study evaluating 2 doses

Regular Approval:

Indication to target all ALK+ NSCLC

Will design a randomized (vs. crizotinib) Phase 3 in crizotinib naïve for broad indication and conversion to Regular Approval. Either ALK master or company sponsored.

Initial BT Request: 5/31/2013

Evaluable ALK+ NSCLC Population	N	ORR% (95%CI)	CR n	PR n
All	21	62	1	12
Prior treatment with crizotinib	16	75 (48,93)	0	12 (5 confirmed)
Prior treatment with crizotinib and ceritinib	3	0	0	0
No prior ALK TKI	2	50	1	0

BT Request denied because: Only 16 patients with ALK+ NSCLC and previously treated with crizotinib were evaluable. Partial responses were observed in 12 of 16 evaluable patients, however only 5 of these responses were confirmed. FDA concluded that while the results were indicative of drug activity, an insufficient number of patients was studied and the follow-up was insufficient to determine duration of response.

Further clinical experience with AP26113

- May 2014, Ariad contacted FDA about re-submission now with data from 57 evaluable ALK+ NSCLC patients.
- FDA responded with some guidance and stated that the new data could potentially support BT designation.
- August 2014, ARIAD resubmitted the breakthrough therapy request.

Updated Efficacy Results

Total of 125 patients treated with a variety of diseases since cut-off of March 2014

Evaluable ALK+ Population	Evalu able	ORR N (%:CI)	CR n	PR n	Confirmed	DoR
All ALK+ (N=71)	61	44 (72%)	1	43	n/a	n/a
All ALK+ NSCLC(N=67)	57	41 (72%:59,83)	1	43	n/a	n/a
Previous crizotinib treated NSCLC (N=61)	51	35 (69%:54,81)	0	35	26	1.6-14.7 months
ALK+ crizotinib-naïve	6	6 (100%)	n/a	n/a	4	1.9 – 12.9 months

Sixty-nine percent (9/13) of patients had regression of their brain metastases following treatment with AP26113.



Safety

Common Adverse Events any grade >10%	Incidence
Nausea	40.0%
Fatigue	34.4%
Diarrhea	33.6%
Cough	25.6%
Headache	24.8%
Vomiting	20.8%
Dyspnea	18.4%
Amylase increased	16.8%
Decreased appetite	16.0%
Constipation	14.4%
Muscle spasms	14.4%
AST increased	13.6%
Peripheral edema	12.8%
Arthralgia	11.2%
Back pain	10.4%
Lipase Increased	10.4%

Serious Adverse Events in ≥ 3 patients	Incidence
Dyspnea	7%
Hypoxia	4%
Pneumonia	4%
Pulmonary Embolism	2%
Pulmonary Symptoms	12/125 (10%) patients
Dyspnea	
Hypoxia	
Dry cough	
Chest tightness	
Pneumonia	
Pneumonitis	

Requirements for BT designation

- Advanced ALK-positive NSCLC is a serious condition with unmet medical need
- Preliminary clinical evidence suggests substantial benefit over *available* therapy
- Safety profile acceptable, however, need more data on pulmonary toxicity
- Recommendation: Grant BT



Breakthrough Therapy Designation Request: Hypothetical Case

Proposed indication:

*Hypothetix for the treatment of advanced unresectable
or metastatic cancers of the hypothetical gland*

April 24, 2015

Hypothetical Malignant Glandularomas (HMG)

- Heterogeneous group of solid tumors
- In 2014, 80,000 new cases and 20,000 deaths from HMG in the U.S.
 - 5-year survival:
 - Stage I: 95% Stage II: 80%, Stage III: 30%, Stage IV: 5-15%
- Treatment options for advanced unresectable or metastatic disease
 - Single-agent chemotherapeutics
 - None demonstrated improved overall survival⁶⁴

FDA-Approved Therapies for Metastatic HMG

Drug (Approval Year)	Clinical Effect
Chemo X (1970's)	Tumor response rate of 10%
Chemo Y (1990's)	<ul style="list-style-type: none"> • Time to tumor growth: Median of 3.5 vs. 1.5 months, HR (95% CI): 0.4 (0.2, 0.5) • Tumor response rate: 20% vs. 8% • Duration of tumor response (95% CI) 5 months (3, 10)

Hypothetix – Mechanism of Action / Rationale

- Monoclonal antibody that binds to HMG-associated protein X (HMG-X) and blocks the interaction with its ligand (HMG-XL)
- Blocking the interaction of HMG-X with HMG-XL modulates downstream signaling events
- Hypothetix decreases proliferation of HMG cell lines in vitro
- Hypothetix reduces tumor size in xenograft models of HMG -- effect is substantially enhanced in combination with Chemotherapy Y

Clinical Data to Support BTB

- Open-label, international, RCT in patients with unresectable and/or metastatic HMG randomized (2:1) to receive as first-line therapy:
 - Hypothetix on Day 1 plus Chemotherapy Y on Day 1 of each 21-day cycle (n=80) OR
 - Chemotherapy Y on Day 1 of each 21-day cycle (n= 40)
- Primary Endpoint: Progression-free survival (PFS)
- Secondary Endpoint: Tumor response rate, duration of tumor response (DOR), overall survival

PFS and Tumor Response Rate

	Hypothetix + Chemo Y N=80	Chemo Y N=42
Progression-free survival		
Events, (%)	45 (56)	30 (71)
Median, mo. (95% CI)	5.5 (2.9, 8.6)	2.7 (1.4, 4.4)
Hazard ratio (95% CI)	0.60 (0.4 – 0.95)	
p-value	0.02	
Tumor response Rate	20%	0
Median DOR, mo. (95% CI)	7.3 (3.4, 9.6)	--

No apparent difference in Overall Survival (OS): median 10.2 months versus 9.6 months, HR=0.94, p=0.72

Subgroup Analyses

- Retrospective testing to identify patients with HMG-XXL (high affinity variant of the ligand, ~25% of patients) demonstrated a median improvement in time to tumor growth of 8 months (HR 0.4) and similar tumor response rate with the Hypothesetix combo
- Time to tumor response analyses based on known prognostic factors for patients with HMG were not consistently in favor of the Hypothesetix combo arm



Safety

	Hypothetix + Chemo Y N=80 %	Chemo Y N=36 %
Neutropenia	50%	25%
Increased ALT	33%	12%
Fatigue	30%	20%
Diarrhea	25%	10%

Division's Recommendations

Denial: Preliminary clinical evidence does not demonstrate substantial improvement over existing therapies

- Although a large relative effect on PFS, absolute magnitude relatively small
- Subset analysis retrospective and based on a small convenience sample
- Add-on trial design: PFS improvement must be balanced with increased toxicities
- Control arm underperformed

Division's Advice

- Conduct a new study stratifying for presence of HMG-XXL and allocating appropriate alpha for this subgroup
- Meet with CDRH regarding validation of HMG-XXL assay

Breakthrough Therapy Designation: Exploring the Qualifying Criteria

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Neurology Drug Case Study

Bimagrumab

Breakthrough Therapy Designation: Exploring the
Qualifying Criteria

April 24, 2015, Washington DC

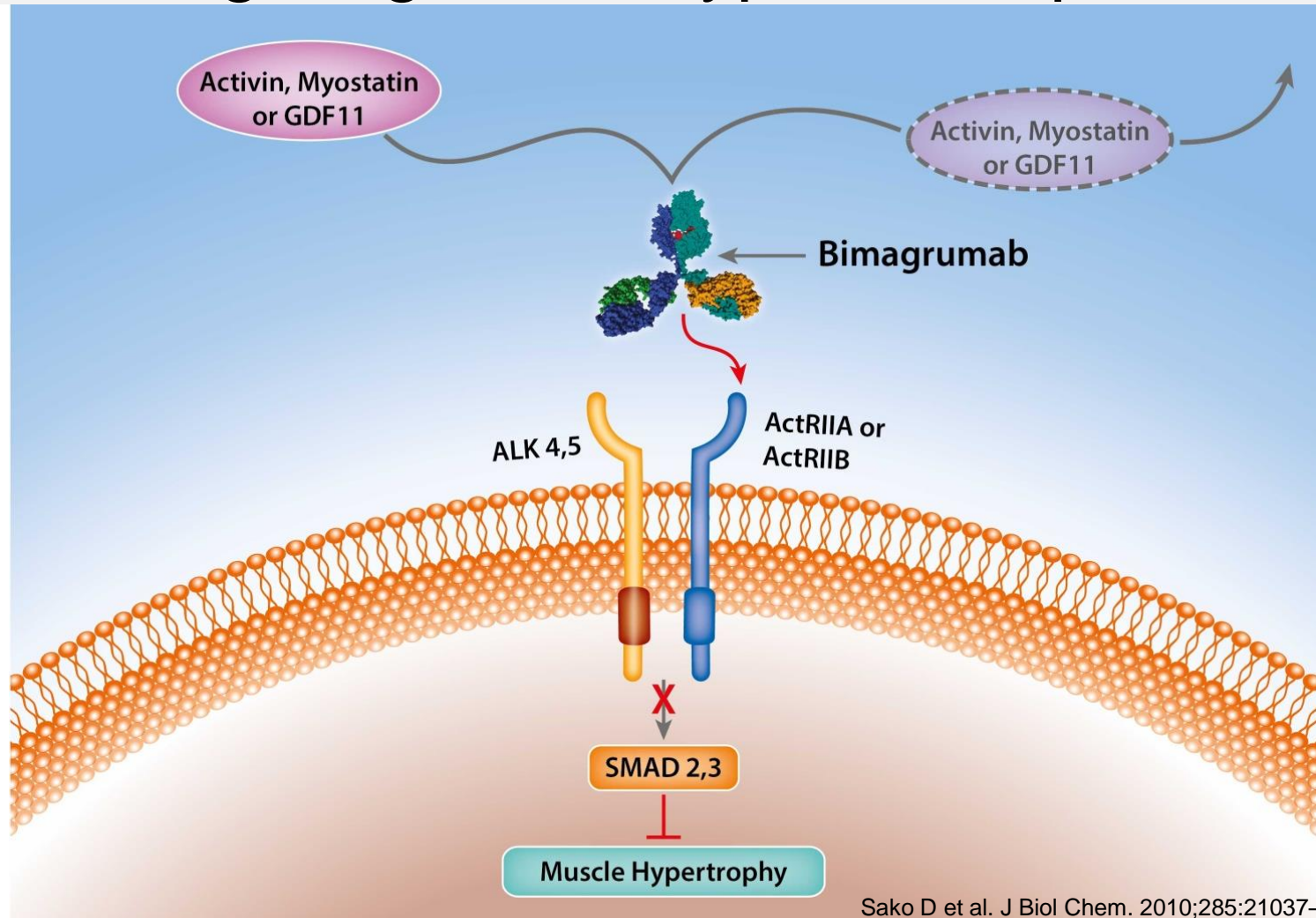
Ronald Farkas, MD, PhD

Clinical Team Leader

Division of Neurology Products

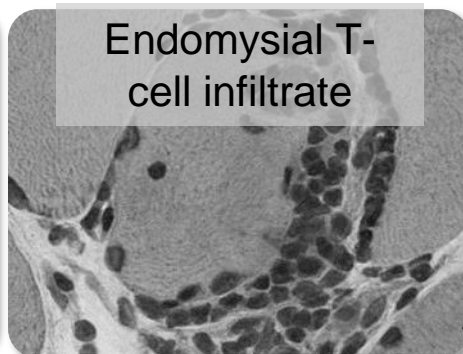
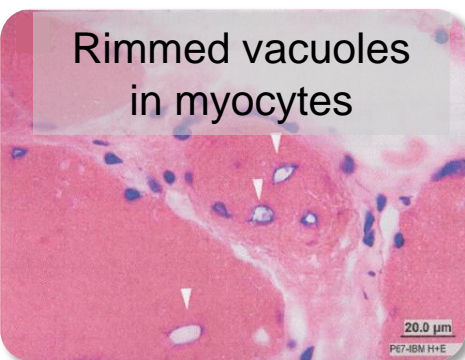
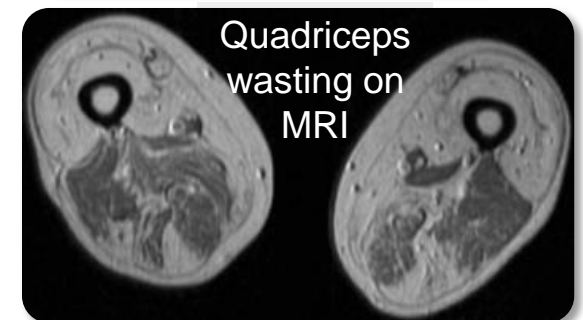
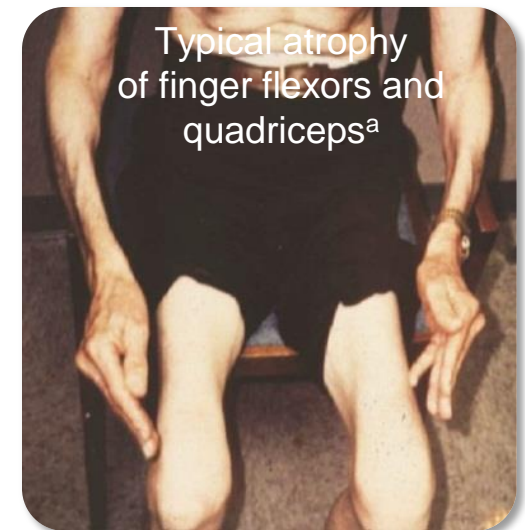
Office of New Drugs/CDER/FDA

Bimagrumab is a human monoclonal antibody targeting activin type II receptors



Sporadic Inclusion Body Myositis (sIBM) is a rare serious disease with no approved treatment

- Progressive debilitating myopathy associated with aging
- Loss of mobility, hand dexterity, swallowing
- Prevalence estimated at 3,000- 20,000 in US
- Pathogenesis not well defined; inflammatory and degenerative components
- Unresponsive to immunosuppression
- No approved treatments



MRI, magnetic resonance imaging.

^aFigure from Engel WK et al. *Neurol.* 2006;66(suppl 1):S20-9.

1. Cox FM et al. *Brain.* 2011;134:3167-75; 2. Benveniste O et al. *Brain.* 2011;134:3176-84; 3. Dalakas MC. *Ann Neurol.* 2008;64:1-3; 4. Dalakas MC. *Curr Opin Pharmacol.* 2010;10:1-7

Acceptable Clinical Endpoints

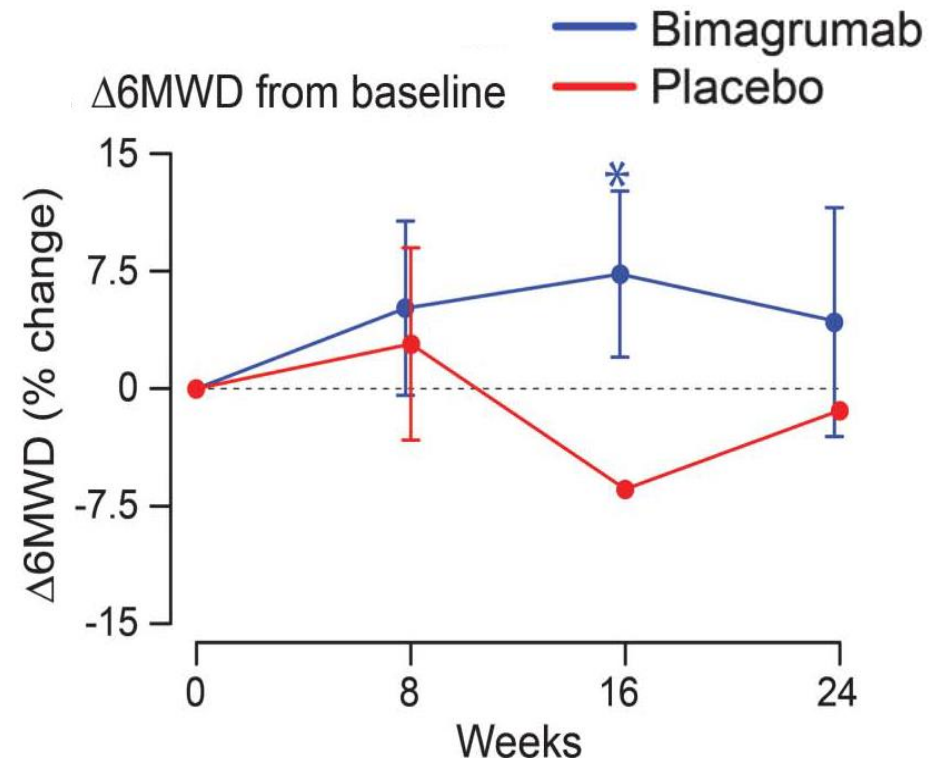
- Ability to perform daily activities
 - e.g. walking, use of hands
- Symptoms
 - e.g. dysphagia
- Decrease in secondary complications
 - e.g. hospitalizations due to aspiration pneumonia
- Other endpoints may be acceptable

Phase IIa Study

- Randomized, placebo-controlled, double-blind
- Single IV infusion of bimagrumab 30 mg/kg
 - 11 patients drug / 3 placebo
- Primary outcome
 - Thigh muscle volume using MRI
 - 8 weeks post infusion
- Secondary outcomes
 - 6 minute walk distance, Timed-up-and-go
 - Quantitative muscle strength, lean body mass

Preliminary Clinical Evidence

- Primary biomarker endpoint:
 - Thigh muscle volume: $p = 0.02$
- Clinical endpoints
 - 6MWT
 - Consistent increase across patients; plausible time course
 - Correlation between muscle volume and functional endpoints
 - No change timed-up-and-go



Additional Evidence

- Positive findings for thigh muscle volume in separate studies in healthy volunteers
- Favorable comparison to expected decline observed in natural history

FDA Decision Considerations

- Walking impairment a key symptom of sIBM
- Phase IIa suggests potential for large, consistent increase in walking ability
 - Randomized control and natural history available
 - Clinical observation supported by consistent tissue/organ-level biomarker findings, including increased muscle volume, within the same patients
- External evidence of pharmacodynamic effect on muscle provided by studies in healthy volunteers
- **Overall high (not total) level of consistency of data**

Sponsor Considerations

- Clinical development program in sIBM already agreed with FDA at the time BTD requested
- BTD requested to benefit from more intensive FDA guidance / FDA senior management involvement in case of future issues
- BTD could help raise awareness about the disease / drug and facilitate recruitment into the subsequent clinical pivotal program
- Unintended regulatory benefit: gain experience with the BTD program, helpful for the preparation of other BTD requests

Sponsor Lessons Learned

- In a disease with very limited clinical trials precedent, natural history data are key to demonstrate “substantial improvement” on a “clinically significant endpoint”
- Individual patient data should show consistency with group summary data, especially in a small study
- In addition to the effect on a clinically significant endpoint, supportive clinical evidence will also be assessed:
 - Supportive endpoints in the same study
 - Consistent target organ findings
 - Data from other studies in healthy volunteers / other diseases



Breakthrough Designation Hypothetical Denial Case Study: *Neurology Drug*

Breakthrough Therapy Designation: Exploring the
Qualifying Criteria
April 24, 2015, Washington DC

Ronald Farkas, MD, PhD
Clinical Team Leader
Division of Neurology Products
Office of New Drugs/CDER/FDA

Disease, Indication, Drug

- Disease:
 - Fulfills criteria for “serious or life-threatening”
 - Unmet medical need exists; no approved drugs
- Indication
 - Rare neurological disease, childhood onset
 - 5,000 affected individuals in U.S.
 - Characterized by progressive weakness
 - Respiratory insufficiency in adulthood
 - Shortened life-span
- Drug- Intended to slow disease progression
 - Pharmacodynamic effect based on genetic defect

Acceptable Endpoints

- Ability to perform daily activities
 - e.g. walking ability, patient-reported ADL's
- Symptoms
 - e.g. shortness of breath
- Decrease in secondary complications
 - e.g. hospitalizations due to pneumonia
- Survival
- Other clinical endpoints may be acceptable
- Most biochemical surrogates in this case problematic because pathophysiology poorly understood

Study Design

- 16-week, randomized, placebo-controlled
- High dose / low dose / placebo
- 30 patients randomized 1:1:1
- Primary Endpoint
 - Biochemical marker of pharmacodynamic effect; not a clear surrogate
- Secondary
 - Pulmonary function tests
 - Hand-held dynamometry
 - Disease-specific patient-reported outcome
 - Timed walk

Preliminary Clinical Evidence

- Some differences across arms in baseline characteristics, such as age and strength
- Low dose: no evidence of efficacy
- High dose
 - Primary biomarker endpoint: negative
 - Clinical endpoints
 - Hand held dynamometry: $p = 0.02$
 - Timed walk: $p = 0.07$
 - Patient-reported outcome: $p = 0.24$
 - Functional vital capacity: numerically inferior

Preliminary Clinical Evidence-2

- If select half of patients with less severe baseline severity
 - Hand-held dynamometry: $p = 0.006$
 - Timed walk: $p = 0.01$
 - Patient-reported outcome: $p = 0.13$
 - Vital capacity: $p = 0.03$

Sponsor Conclusions

- Biomarker findings
 - Negative due to technical factors; non-contributory
- Positive clinical findings support designation
 - Study suggests dynamometry the best endpoint
- Subset analysis
 - Supported by drug mechanism and pathophysiology
 - Highly statistically significant
 - Multiple positive endpoints confirm efficacy

FDA Considerations

- Negative biomarker
 - *Increases concern that drug may not have intended pharmacodynamic effect*
- Problematic to try to ‘rescue’ negative study by considering *Clinical endpoints* if *biomarker* negative or *Biomarker endpoints* if *clinical primary* negative
 - When data very limited, consistency of findings critical

Clinical Endpoint Considerations

- Reasonable to design phase 2 study to learn about clinical endpoint performance
 - Consistent with overall exploratory goals
- But inflation of type 1 error from multiple-testing no less a factor
 - Multiplicity a concern even for pre-specified primary if *statistical analysis* not clearly pre-specified
 - No reliable way to determine if nominally positive results due to chance
 - Endpoints that lean against efficacy very worrisome

Clinical Endpoint Considerations-2

- Post-hoc subsets may appear reasonable, but multiplicity a dominant factor
 - e.g. if results had favored more advanced patients, similar argument could be made
 - ***Even very small p-values not interpretable***
- “Consistency of findings” across endpoints can arise even when drug ineffective, e.g.
 - Endpoints can measure same difference between arms that arose by chance, for example from baseline imbalances
 - Common in small studies (and subsets of small studies)
 - Other “true” differences that arise from non-random dropout, unblinding, etc

Breakthrough Therapy Designation: Exploring the Qualifying Criteria

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Breakthrough Therapy - Tafenoquine

**Breakthrough Therapy Designation:
Exploring the Qualifying Criteria**

April 24, 2015

Tafenoquine

- 8-aminoquinoline, antimalarial drug
 - synthetic analogue of primaquine
- Has activity against all stages of the *Plasmodium vivax* lifecycle, including the dormant liver stage, hypnozoite
- Slow clearance of blood stage therefore requires co-administration with another faster acting blood schizonticide e.g. chloroquine

Plasmodium vivax malaria

- Vivax malaria is a serious disease
- 130 - 390 million cases annually worldwide
- *P. vivax* has complex life-cycle: includes a dormant liver stage i.e., hypnozoite stage
 - activation of hypnozoites leads to relapse of malaria
- Treatment and radical cure : Chloroquine and Primaquine 15 to 30mg daily x 14 days
- FDA approved primaquine (15mg) in 1952

Tafenoquine

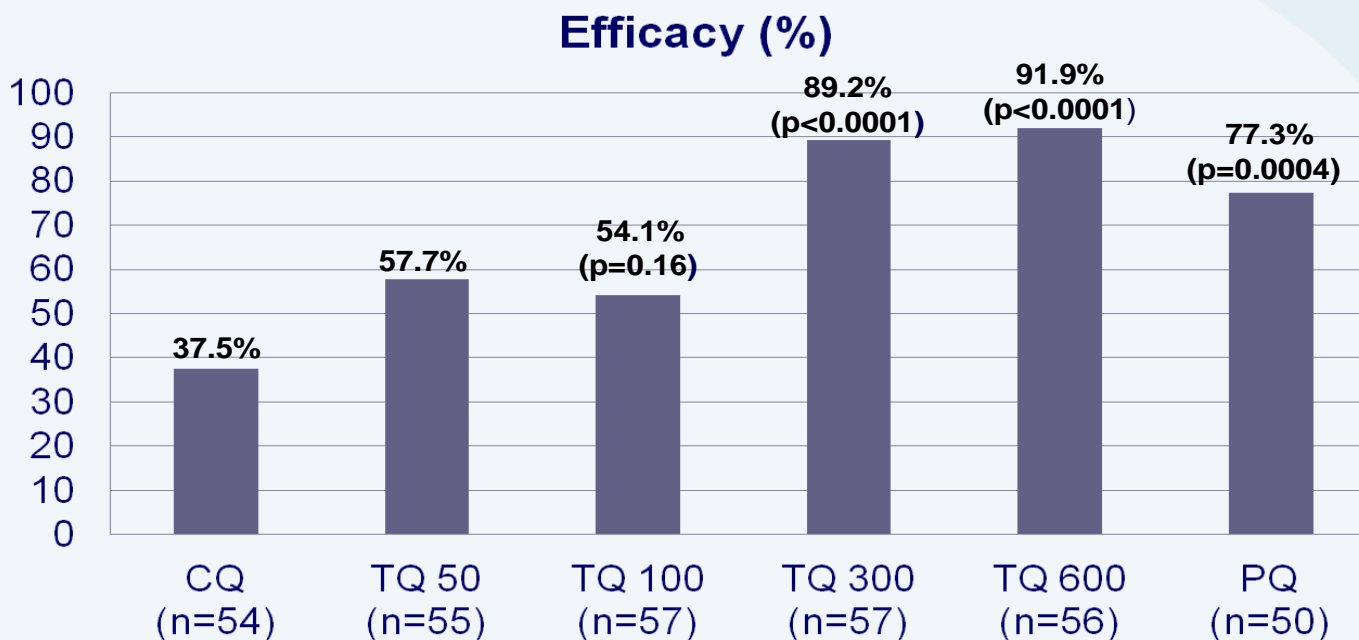
- Sponsor requested Breakthrough Therapy designation on October 31, 2013 during phase 2 development
 - Indication: Treatment and relapse prevention (radical cure) of *Plasmodium vivax* malaria
- End-of-phase 2 meeting, November 17, 2013: Discussed phase 2 clinical trial results and proposed phase 3 clinical development
- Breakthrough Therapy designation, December 18, 2013
- CDER Medical Policy Council was briefed on tafenoquine

Clinical Trials – Phase 2

- Results from three phase 2 trials were submitted to support the sponsor's request for breakthrough designation
- Phase 2b trial (TAF112582): A multi-center, double-blind, randomized, active-control, dose-ranging study to evaluate the efficacy, safety and of **chloroquine (CQ) + tafenoquine (50 to 600 mg) single dose vs. CQ alone vs. CQ + primaquine (PQ)** in 329 adults with malaria due to *P. vivax*

Primary Efficacy Results Show Convincing Efficacy at TQ 300mg and 600mg Doses

(Relapse-free Efficacy at 6 months: Kaplan Meier Estimates)



Treatment Difference (95% CI) vs CQ (target = 30%):

TQ 600: 54.5% (38%,71%) TQ 300: 51.7% (35%,69%)

TQ 100: 16.6% (-3%,36%) TQ 50: 20.3% (0%,40%)

PQ: 39.9% (21%,59%)

Clinical Trials - Phase 2

- Open-label, dose-ranging
- 7 dose regimens of tafenoquine ranging from total doses of 500mg to 3000mg vs. CQ+ PQ vs. CQ alone
 - Relapse rate for CQ+ TQ (0 to 13%)
 - Relapses across treatment arms: CQ+TQ 4%; CQ alone 71%; CQ+PQ 25%
- Randomized, active-control, double-blind
- TQ 400mg x 3 days vs. CQ+PQ(15mg) x 14 days
 - TQ monotherapy: exhibited slow parasite and slow fever clearance - (combination with CQ necessary)
 - TQ: 100% relapse-free up to 120 days

Rationale for Breakthrough Designation

- Vivax malaria is a serious disease
- Preliminary clinical evidence demonstrates that tafenoquine provides substantial improvement over primaquine
- Tafenoquine provides an alternative treatment option with shorter dosing regimen
- Single-dose therapy should improve compliance compared to a 7 to 14 day course of primaquine



A Case Study NaBen for the Treatment of Negative Symptoms of Schizophrenia

Breakthrough Therapy Designation: Exploring the
Qualifying Criteria

April 24, 2015, Washington DC

Lucas Kempf, MD

Clinical Team Leader

Division of Psychiatry Products

Office of New Drugs/CDER/FDA

Content of Presentation

- Schizophrenia: disease overview
- Treatment Overview
- Product Description
- Summary of Clinical Evidence
- Division Discussion
- FDA Rationale

Schizophrenia Overview

- Schizophrenia is a common (1% of the population) serious syndrome
- It is characterized by positive symptoms
 - Hallucinations, delusions and thought disorder
- Negative symptoms
 - Flat affect, anhedonia, amotivation, ambivalence
- Cognitive disorder
 - Decrease in general IQ, planning, memory, processing speed and other domains

Treatments Overview

- Current treatments target Dopamine receptors and primarily improve positive symptoms with little improvement of negative or cognitive symptoms
- There are no current targeted treatment for negative symptoms or cognitive treatments
- Sponsor asked for breakthrough designation for negative symptoms based on a single study

Original Investigation

Add-on Treatment of Benzoate for Schizophrenia A Randomized, Double-blind, Placebo-Controlled Trial of D-Amino Acid Oxidase Inhibitor

Hsien-Yuan Lane, MD, PhD; Ching-Hua Lin, MD, PhD; Michael F. Green, PhD; Gerhard Helleman, PhD;
Chih-Chia Huang, MD, PhD; Po-Wei Chen, MD; Rene Tun, MD; Yue-Cung Chang, PhD; Guochuan E. Tsai, MD, PhD

- Randomized, double blind, placebo controlled trial in 52 patients with chronic schizophrenia on stable symptoms and stable doses for minimum of 3 months with a minimal PANSS score of 60
- Six week trial of add-on of 1g/d sodium benzoate or placebo
- Primary outcome measure was the Positive and Negative Syndrome Scale (PANSS)
- Additional outcome measures were cognition and scales for the Assessment of Negative Symptoms, Global assessment of Function, Quality of Life Scale, Hamilton Depression Rating Scale, and Clinical Global Impression and MATRICS Consensus Cognitive Battery

From: **Add-on Treatment of Benzoate for Schizophrenia: A Randomized, Double-blind, Placebo-Controlled Trial of d-Amino Acid Oxidase Inhibitor**

JAMA Psychiatry. 2013;70(12):1267-1275. doi:10.1001/jamapsychiatry.2013.2159

Table 2. Clinical Measures of the Positive and Negative Syndrome Scale (PANSS) During the 6-Week Treatment^a

Scale and Treatment Group	Mean (SD)				Difference in Score Changing Rate vs Placebo, Mean (SE)	t_{146} Value	P Value	Effect Size (Cohen d)
	Baseline	Week 2	Week 4	Week 6				
Total					-2.1 (0.3)	-7.6	<.001	1.53
Placebo	87.3 (8.6) (n = 27)	84.3 (10.3) (n = 27)	83.1 (9.6) (n = 24)	81.4 (10.0) (n = 23)				
Benzoate	90.3 (16.3) (n = 25)	82.4 (13.9) (n = 25)	76.5 (12.8) (n = 25)	71.7 (14.3) (n = 24)				
Positive subscale					-0.6 (0.1)	-7.4	<.001	1.69
Placebo	20.4 (4.4)	20.0 (4.7)	19.5 (4.2)	18.8 (4.1)				
Benzoate	20.6 (3.6)	18.4 (3.4)	17.0 (3.3)	15.3 (3.4)				
Negative subscale					-0.6 (0.1)	-6.2	<.001	1.19
Placebo	24.8 (3.6)	23.9 (3.9)	23.4 (3.4)	23.1 (3.6)				
Benzoate	26.1 (6.9)	24.0 (6.1)	22.1 (5.6)	20.8 (6.0)				
General psychopathology subscale					-0.9 (0.2)	-5.7	<.001	1.16
Placebo	42.2 (4.7)	40.4 (5.3)	40.3 (5.2)	39.6 (5.7)				
Benzoate	43.6 (8.2)	40.0 (7.0)	37.4 (6.5)	35.7 (7.2)				

^a Mixed-model repeated-measure methods with treatment, week, and treatment-week interaction as the fixed effects and intercept as the random effect; baseline value was the covariant. An autoregressive covariance matrix was fit to the within-patient repeated measures. *P* values were based on 2-tailed tests.

Table Title:

Clinical Measures of the Positive and Negative Syndrome Scale (PANSS) During the 6-Week Treatment^a

From: **Add-on Treatment of Benzoate for Schizophrenia: A Randomized, Double-blind, Placebo-Controlled Trial of d-Amino Acid Oxidase Inhibitor**

JAMA Psychiatry. 2013;70(12):1267-1275. doi:10.1001/jamapsychiatry.2013.2159

Table 3. Clinical Measures of SANS, CGI, GAF, QOLS, and HDRS During the 6-Week Treatment^a

Scale and Treatment Group	Mean (SD)				Difference in Score Changing Rate vs Placebo, Mean (SE)	t_{146} Value	P Value	Effect Size (Cohen <i>d</i>)
	Baseline	Week 2	Week 4	Week 6				
SANS					-2.0 (0.2)	-8.01	<.001	1.56
Placebo	55.0 (13.1) (n = 27)	52.6 (12.8) (n = 27)	52.0 (12.4) (n = 24)	51.3 (12.4) (n = 23)				
Benzoate	59.2 (14.2) (n = 25)	52.5 (13.9) (n = 25)	46.7 (13.4) (n = 25)	42.5 (14.6) (n = 24)				
GAF					1.1 (0.2)	6.07	<.001	1.2
Placebo	41.4 (7.8)	42.5 (7.9)	43.5 (7.9)	45.2 (8.3)				
Benzoate	40.6 (8.6)	44.4 (8.4)	48.0 (8.4)	51.5 (8.7)				
QOLS					1.1 (0.2)	6.88	<.001	1.5
Placebo	16.4 (7.4)	18.2 (7.5)	19.5 (7.2)	20.8 (6.8)				
Benzoate	15.4 (10.0)	19.6 (9.8)	23.3 (9.2)	26.8 (10.9)				
CGI					-0.1 (0.02)	-4.9	<.001	1.21
Placebo	4.5 (0.8)	4.4 (0.8)	4.4 (0.8)	4.3 (0.8)				
Benzoate	4.6 (0.6)	4.1 (0.8)	3.6 (0.7)	3.5 (0.7)				
HDRS					-0.3 (0.1)	-3.55	<.001	0.74
Placebo	6.3 (4.0)	5.7 (3.8)	5.6 (4.2)	5.2 (3.5)				
Benzoate	7.1 (5.4)	5.3 (4.7)	4.4 (3.8)	3.8 (3.1)				

Abbreviations: CGI, Clinical Global Impression; GAF, Global Assessment of Function; HDRS, Hamilton Depression Rating Scale-17 items; QOLS, Quality of Life Scale; SANS, Scales for the Assessment of Negative Symptoms-20 items.

^a Mixed-model repeated-measure methods with treatment, week, and

treatment-week interaction as the fixed effects and intercept as the random effect; baseline value was the covariance. An autoregressive covariant matrix was fit to the within-patient repeated measures. *P* values were based on 2-tailed tests.

Table Title:

Clinical Measures of SANS, CGI, GAF, QOLS, and HDRS During the 6-Week Treatment^a

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JAMA Psychiatry. 2013;70(12):1267-1275. doi:10.1001/jamapsychiatry.2013.2159

Table 4. Cognitive Measures in 7 Domains Recommended by the Measurement and Treatment Research to Improve Cognition in Schizophrenia Committee During the 6-Week Treatment^a

Cognitive Domain and Treatment Group	Mean (SD)		Least Squares, Mean (SE) Change in Benzoate-Placebo	t Value	P Value ^{a,b}	Effect Size (Cohen d)
	Baseline	End Point				
Speed of processing			3.2 (1.4)	2.3	0.03	0.65
Placebo (n = 25)	49.3 (9.2)	50.0 (8.1)				
Benzoate (n = 22)	50.8 (11.0)	54.7 (13.9)				
Attention/vigilance			2.3 (2.5)	0.93	0.36	0.27
Placebo (n = 26)	50.2 (10.5)	50.2 (10.2)				
Benzoate (n = 23)	49.8 (9.6)	52.1 (7.9)				
Working memory			0.2 (1.9)	0.12	0.91	0.04
Placebo (n = 23)	47.2 (7.1)	47.6 (7.9)				
Benzoate (n = 22)	53.0 (11.8)	53.7 (12.5)				
Verbal learning and memory			3.4 (2.5)	1.37	0.18	0.39
Placebo (n = 26)	49.2 (9.1)	54.1 (9.4)				
Benzoate (n = 23)	51.0 (11.1)	59.4 (12.4)				
Visual learning and memory			6.3 (2.6)	2.44	0.02	0.7
Placebo (n = 25)	49.0 (8.0)	52.9 (10.3)				
Benzoate (n = 23)	51.1 (11.9)	61.2 (14.2)				
Reasoning and problem solving			1.0 (2.3)	0.43	0.67	0.12
Placebo (n = 26)	50.2 (9.9)	55.4 (8.5)				
Benzoate (n = 23)	49.8 (10.4)	56.1 (8.0)				
Social cognition			-0.1 (3.8)	-0.02	0.98	<0.01
Placebo (n = 20)	46.9 (6.5)	50.0 (9.6)				
Benzoate (n = 19)	53.3 (12.0)	56.2 (11.3)				
Global composite score ^b			2.9 (1.9)	1.49	0.15	0.51
Placebo (n = 17)	47.4 (8.6)	50.9 (8.6)				
Benzoate (n = 17)	52.6 (10.9)	59.0 (12.3)				
Neurocognitive composite ^c			3.7 (1.7)	2.19	0.04	0.67
Placebo (n = 22)	48.9 (9.6)	52.8 (9.6)				
Benzoate (n = 20)	51.3 (10.5)	58.9 (12.8)				

^a Mixed-model repeated-measure methods, adjusted for age, sex, educational level, treatment, and visit times.

^b For assessing the global composite, an overall composite T score that included all 7 domains was calculated by standardizing the sum of T scores.

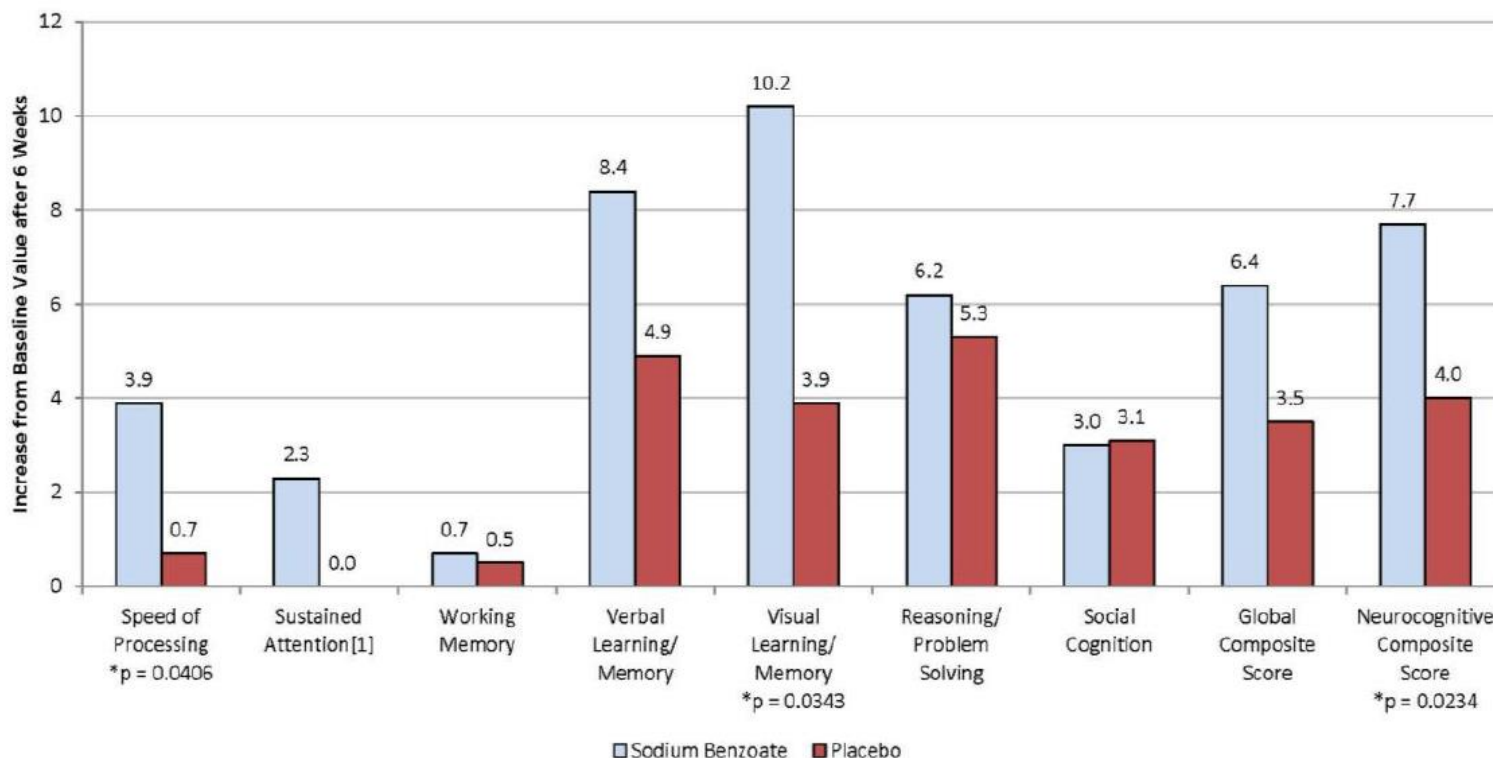
^c For assessing neurocognitive ability, an overall composite T score that included all 6 neurocognitive domains, excluding social cognition, was calculated by standardizing the sum of T scores.

Table Title:

Cognitive Measures in 7 Domains Recommended by the Measurement and Treatment Research to Improve Cognition in Schizophrenia Committee During the 6-Week Treatment^a

Clinical Evidence

Figure 6 Mean Changes, Cognitive Function after Six Weeks of Therapy



Only paired values were used in the computation of percent change from baseline
All p-values obtained using nonparametric model

Division Discussion

- The division has previously outlined an approval pathway for Negative symptoms of schizophrenia in the publication *Laughren T, Levin R. Food and Drug Administration perspective on negative symptoms in schizophrenia as a target for a drug treatment claim. Schizophr Bull. 2005;32:220–222.*
- It is clearly stated that for a Negative symptom claim the therapy should only improve **Negative** symptoms and if it improved **all** aspects of the illness it would be considered a “**broad**” treatment of schizophrenia.

FDA Rationale

- Because of the effects on positive, negative and cognitive symptoms, we denied the narrow Negative Symptoms Indication
- Ask sponsor to amend application to apply for Adjunctive “Broad” treatment of schizophrenia
- Highly significant results with a relatively large effect size when compared to previous antipsychotic studies
- Relatively Benign side effect profile



Breakthrough Therapy designation – A Case Study

**LentiGlobin BB305 Drug Product for the treatment of
transfusion-dependent patients with β -thalassemia major**

April 24, 2015

Ilan Irony, MD – Chief, General Medicine Branch –

DCEPT, OCTGT, CBER, FDA

Anne-Virginie Eggimann, M.Sc. – Vice President,

Regulatory Science – bluebird bio, Inc.

Content of Presentation

- Beta thalassemia major: disease overview
- Product Description
- Summary of clinical evidence
- Sponsor's lessons learned
- FDA considerations

β-Thalassemia Major: Disease Overview

Disease

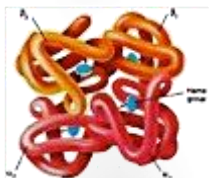
- β-thalassemia major (e.g. transfusion-dependent)
- Monogenic, severe anemia
- Loss of or reduced β-globin production
- Poor quality of life and shortened lifespan

Current Treatments

- Standard of care: frequent, chronic transfusions
→ iron overload and organ failure; iron chelation suboptimal
- Allogeneic transplant (rarely used)
 - Finding a suitable match
 - Morbidity/mortality with graft rejection, graft versus host disease and immunosuppression

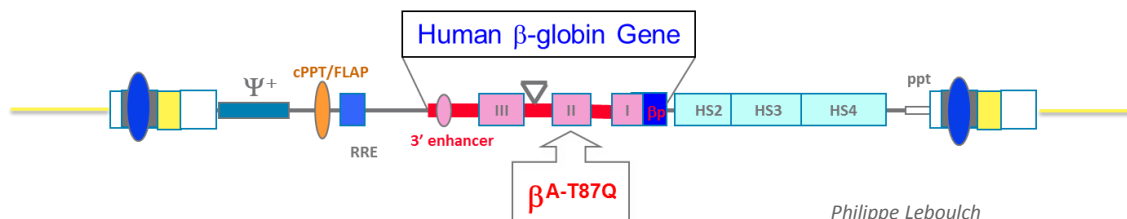
Epidemiology

- Global prevalence ~288K; incidence ~60K
- Rare disease in the US and the EU
- Affects people of Mediterranean, Middle Eastern, South Asian and SE Asian descent

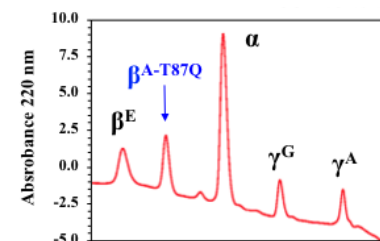


Product Description

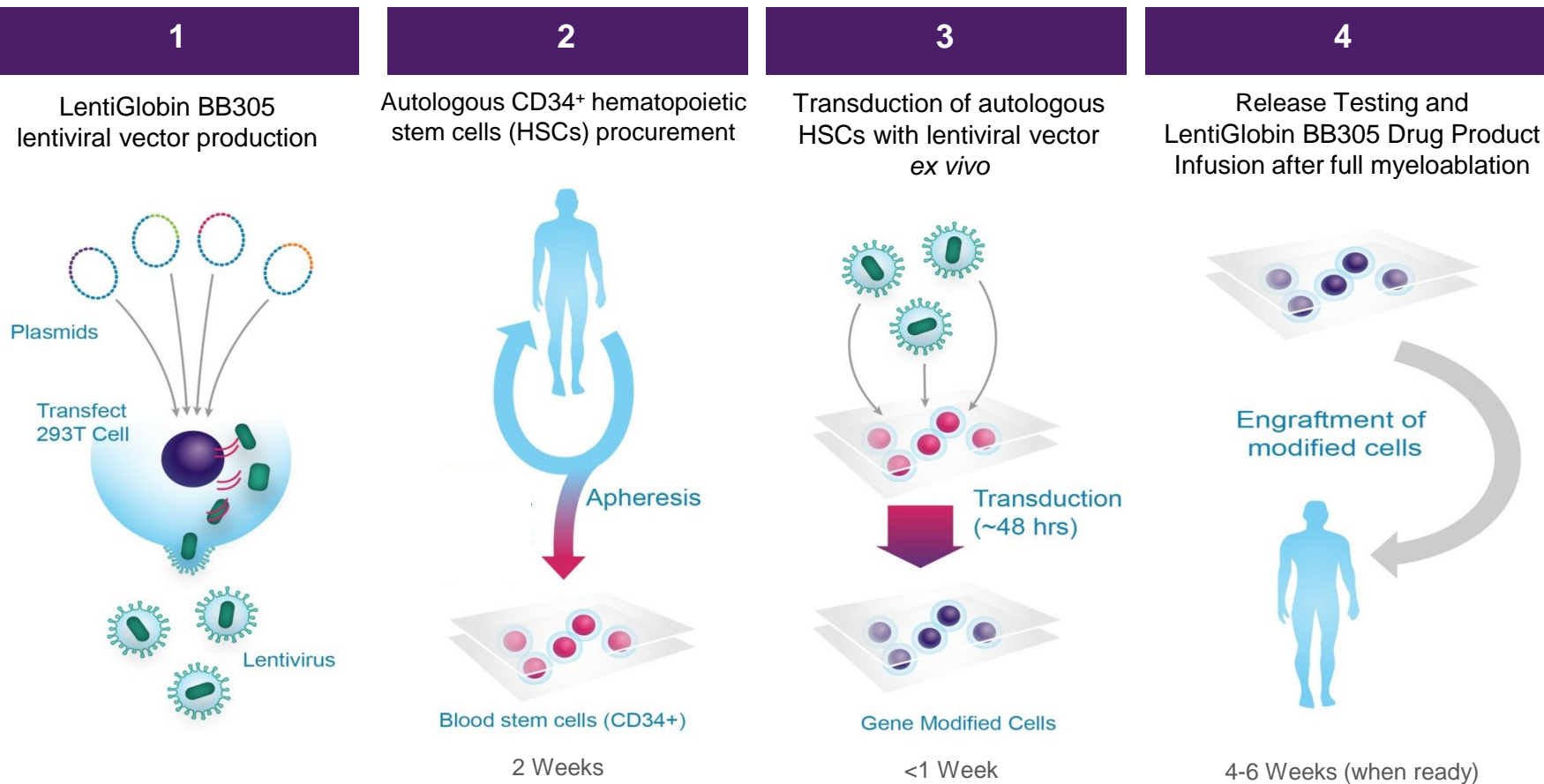
- LentiGlobin BB305 Drug Product (DP) consists of autologous CD34⁺ hematopoietic stem cells transduced with LentiGlobin BB305 lentiviral vector encoding the human β^{A-T87Q} -globin gene
- LentiGlobin BB305 DP is a gene therapy product developed for the treatment of β -thalassemia and sickle cell disease
 - *Presentation today will focus solely on β -thalassemia and efficacy data*



IN-VIVO BIOMARKER

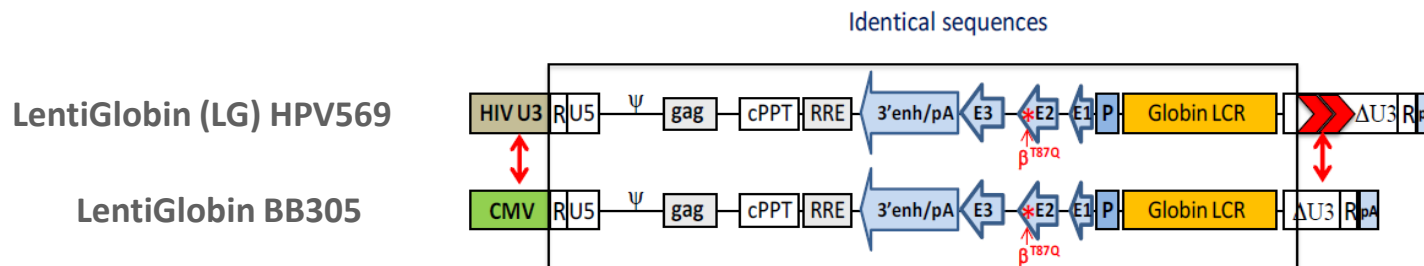


LentiGlobin BB305 Drug Product Overview



Clinical Evidence - Initial BT Application

- 3 subjects treated with a previous product (LentiGlobin HPV569 Product) and nonclinical comparison between lentiviral vectors:
 - One transfusion independent by 1 year post-transplant sustained 5 years
 - One did not engraft and received back-up cells
 - One remained transfusion dependent
- FDA denial: ***“in the absence of any clinical data with LentiGlobin BB305 Drug Product, requirement for preliminary clinical evidence is not fulfilled.”***
- FDA commented that the proposed endpoint for clinical evidence was promising and clinically significant for β -thalassemia major



Clinical Evidence – Revised BT Application

Data from Treated Subjects with β -thalassemia in On-going Phase 1/2 Clinical Studies

TRIAL	HGB-204 (Multi-center USA, Thailand, Australia) (NCT01745120) Under IND					HGB-205 Single center in France (NCT02151526)	
Subject	1102	1104	1106	1107	1108	1201	1202
Age/Sex	18/F	21/F	20/F	26/F	18/F	18/F	16/M
Genotype	$\beta 0/\beta E$	$\beta 0/\beta E$	$\beta 0/\beta 0$	$\beta 0/\beta 0$	$\beta 0/\beta +$	$\beta 0/\beta E$	$\beta 0/\beta E$
Transfusion requirement (mLs/kg/year)	137	153	197	223	144	139	188

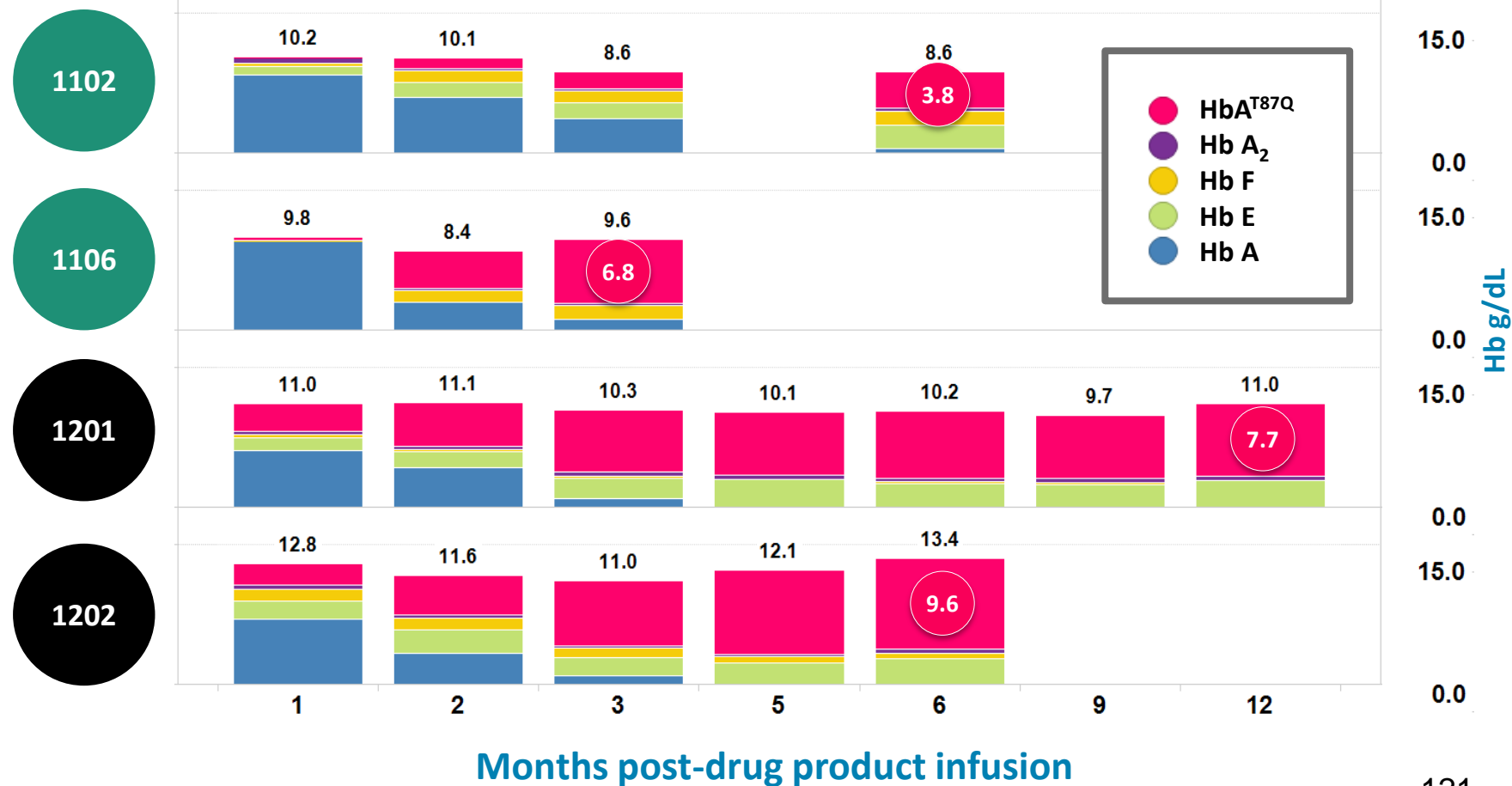
Demographics and Baseline Characteristics data presented in Dec. 2014 at Annual American Society of Hematology (ASH) meeting

HGB-204 is planned to enroll 15 subjects; HGB-205 is planned to enroll 7 subjects.

Clinical Evidence – Revised BT Application

β A-T87Q-globin production – LentiGlobin BB305

Subject

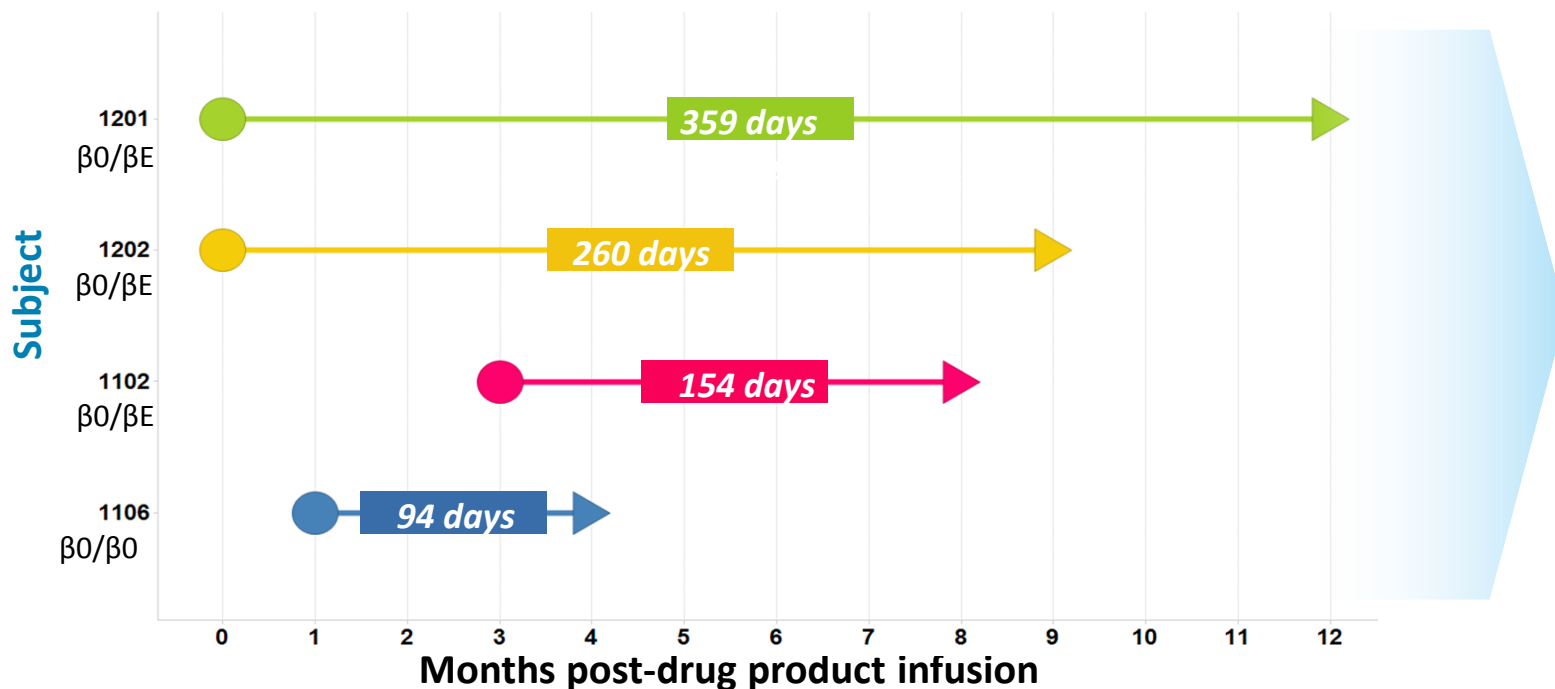


Data as of December 1, 2014 from an open database and is subject to change

Clinical Evidence – Revised BT Application

Days Transfusion-Free

as of December 1, 2014

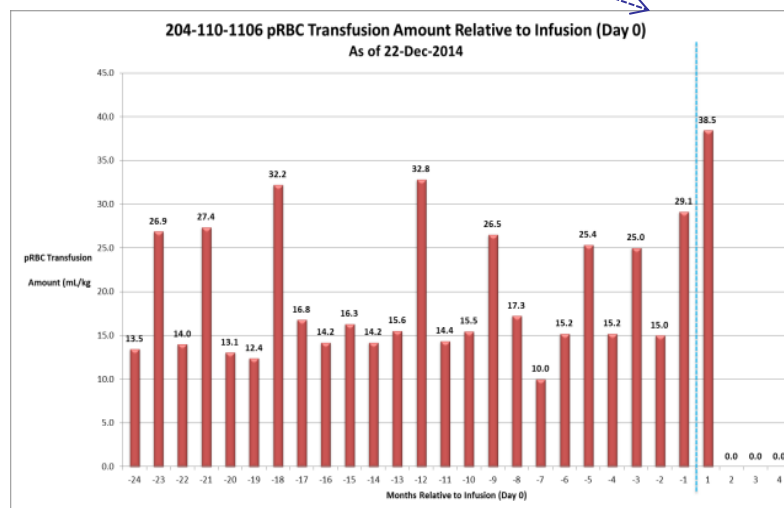
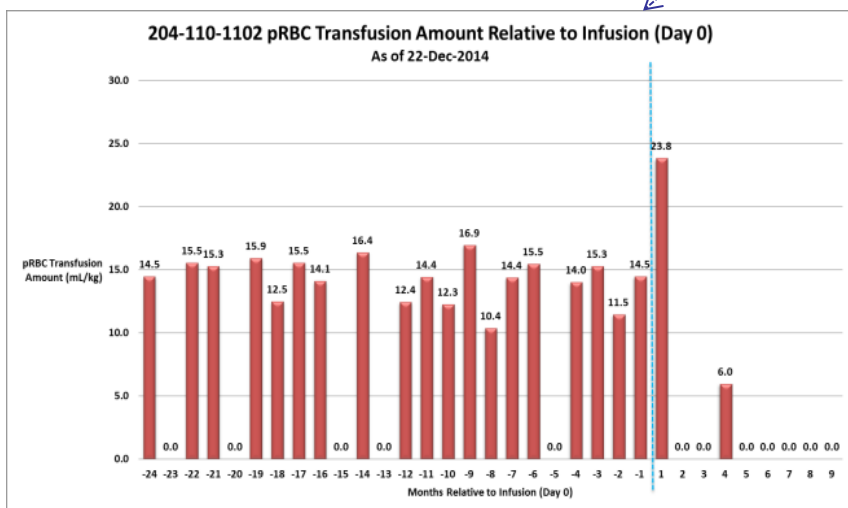


All subjects with at least 3 months of follow-up were transfusion-free, regardless of genotype

Clinical Evidence – Revised BT Application

- In addition to data in previous slides, during review of the new BT application, FDA asked for an update on latest clinical data (any new patients treated, update on progress of patients treated) and for comparison of transfusion requirements before and after treatment
- bluebird bio provided a graphical representation of the transfusion amount (ml/kg) per months starting 2 years before infusion for three HGB-204 subjects

Blue line refers to timing of drug product infusion



FDA Considerations

- Considerations for clinical evidence in rare diseases, such as β -thalassemia, are different than in common diseases: magnitude of effect, rather than formal statistical analyses
- Gene therapy products are often modified during clinical development prior to Phase 3. Establishing comparability between different versions of the product can be challenging.

Breakthrough Therapy Designation: Exploring the Qualifying Criteria

Park Hyatt Hotel • Washington, DC
Friday, April 24, 2015